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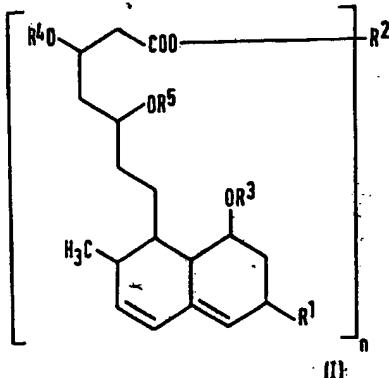
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(54) Compounds Which Inhibit
 Cholesterol Biosynthesis, and Their
 Preparation

(57) Compounds of formula (I):



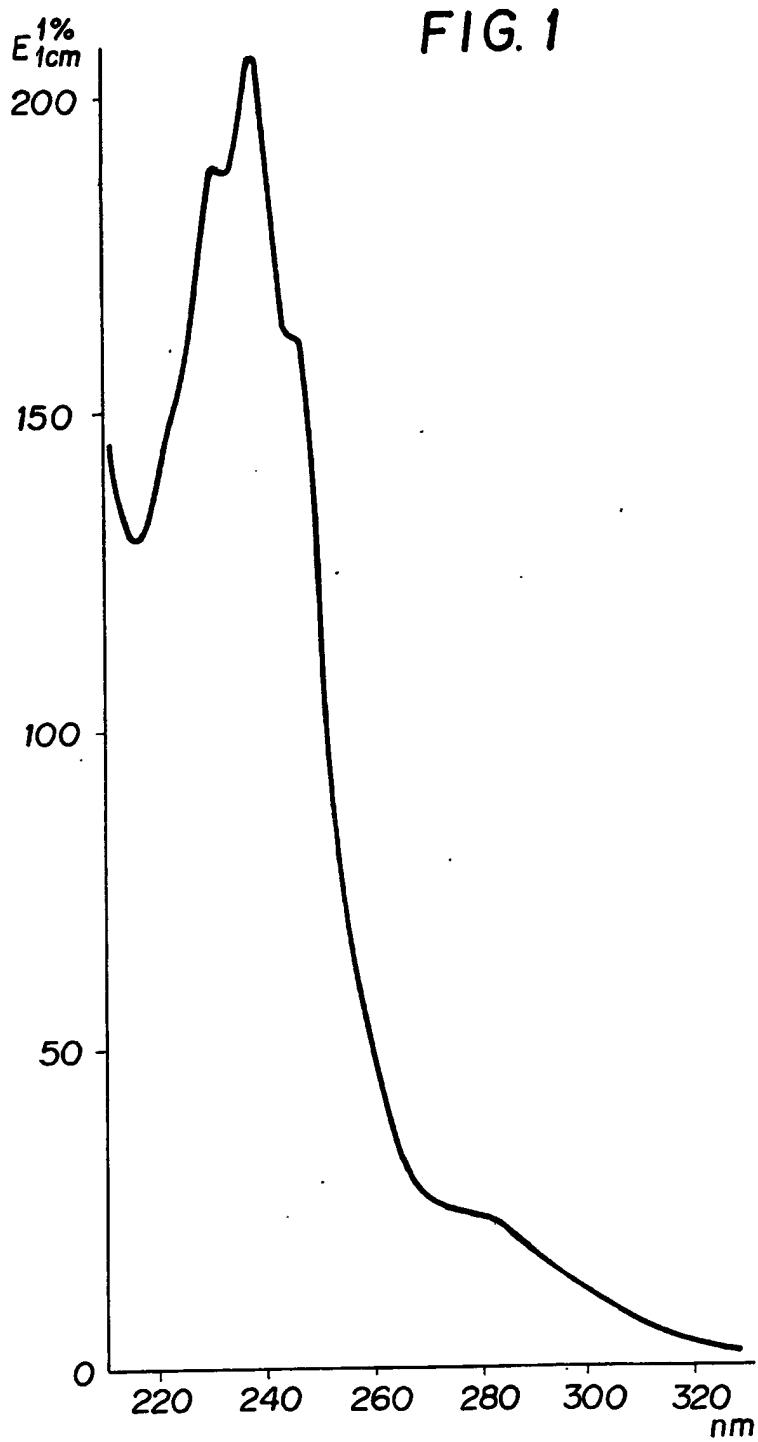
(wherein R¹ represents a hydrogen atom or a methyl group; R² represents a hydrogen atom, the alcoholic moiety of an ester or the cationic moiety of a salt; R³, R⁴ and R⁵ are the same or different and each represents a hydrogen atom or an organic or inorganic acyl group, provided that, when R³ represents a 2-methylbutyryl group, R⁴ and R⁵ both represent acyl groups; and n is the valency of R²) may be prepared by cultivating microorganisms of the genera *Penicillium* or *Monascus* or by saponifying or esterifying the corresponding carboxylic acid or lactone or, in the case of esters of the above formula (I), by esterifying a corresponding salt of the above formula (I).

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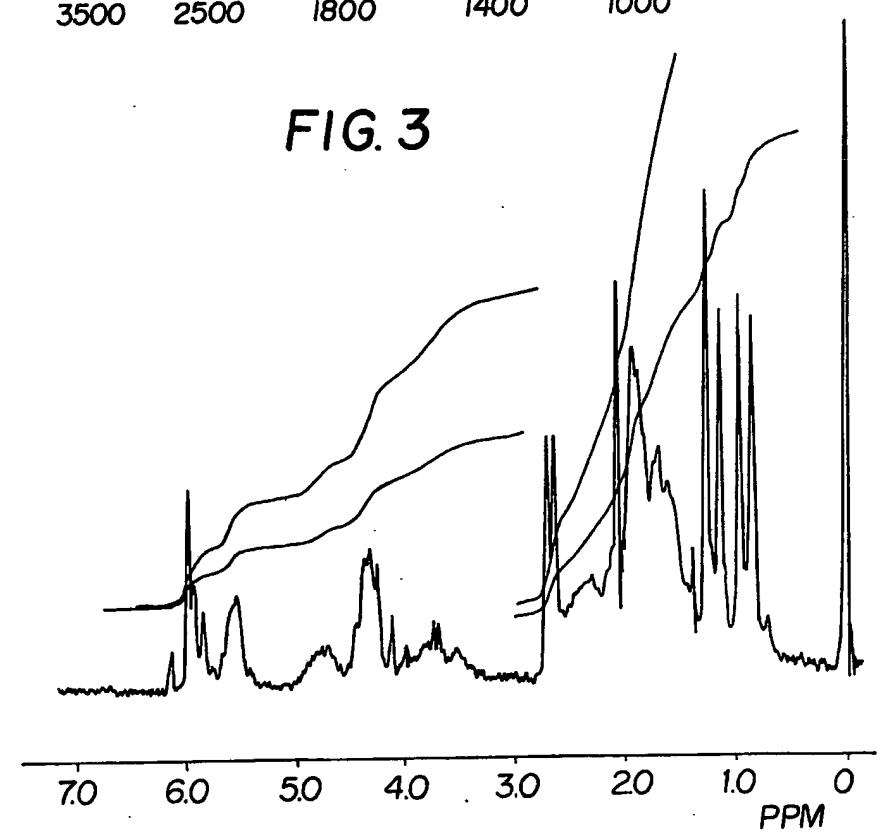
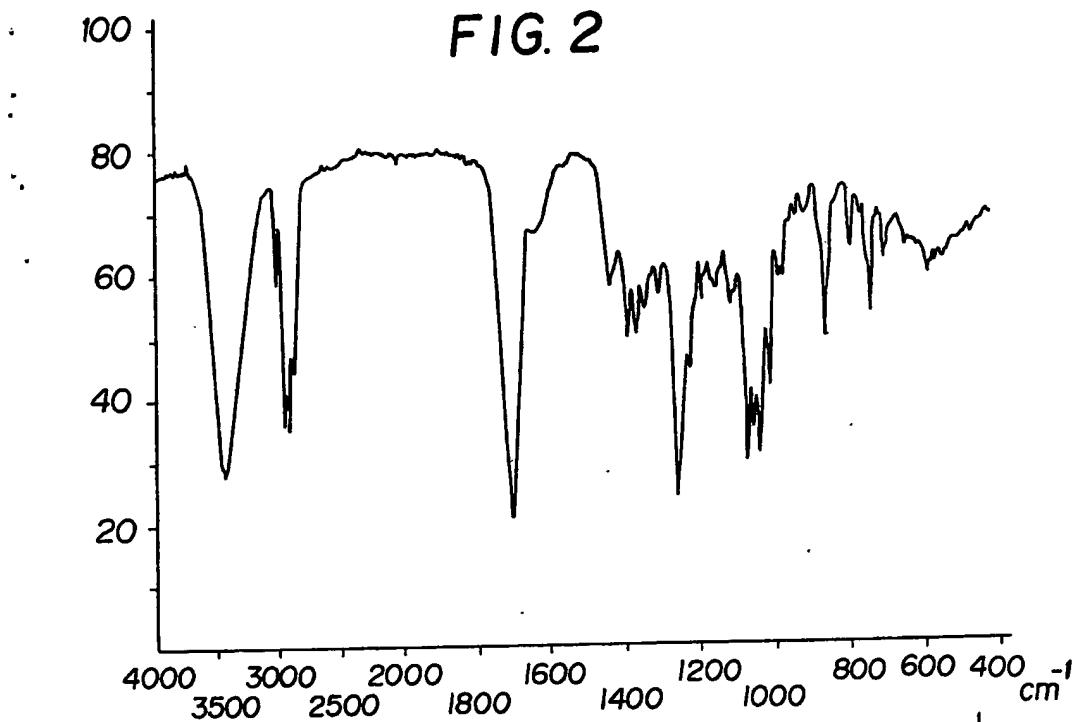
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FIG. 1



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z/2



SPECIFICATION
Compounds Which Inhibit Cholesterol Biosynthesis, and Their Preparation

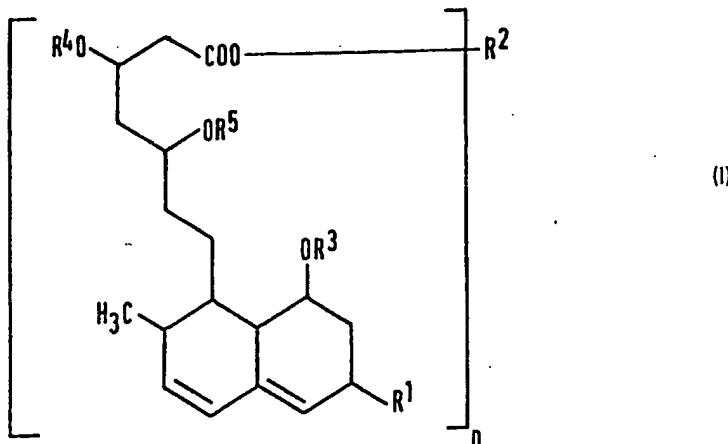
The present invention relates to a series of novel compounds which have been found to inhibit cholesterol biosynthesis and which can thus be used in the treatment and prevention of disorders arising from high levels of cholesterol in the body. The invention also provides processes for preparing these compounds. 5

Hyperlipaemia, especially hypercholesterolaemia, is known to be one of the main causes of cardiopathy, such as cardiac infarction or arteriosclerosis. As a result, considerable research has been carried out in an effort to discover compounds capable of reducing lipid, and especially cholesterol, 10 levels in the blood. A group of compounds of this type is disclosed in US Patent Specification No. 3,983,140 and was isolated from microorganisms of the genus *Penicillium*; this group of compounds is collectively designated ML-236. Also, United Kingdom Patent Applications No. 2046737 and No. 2049664 disclose a structurally similar compound designated Monacolin K or MB-530B, and certain salts and esters of MB-530B are disclosed in United Kingdom Patent Application No. 2055100. 15

MB-530B and its salts may be prepared by cultivating microorganisms of the genus *Monascus*, especially, but not exclusively, strains of *Monascus ruber*. Another compound of the MB-530 group, designated MB-530A, as well as other compounds related to the ML-236 and MB-530 groups are disclosed in our co-pending United Kingdom Patent Application No. 8110075.

We have now discovered a series of compounds related to the ML-236 and MB-530 groups 20 which also have valuable inhibitory activity against the biosynthesis of cholesterol.

The compounds of the invention have the formula (I):

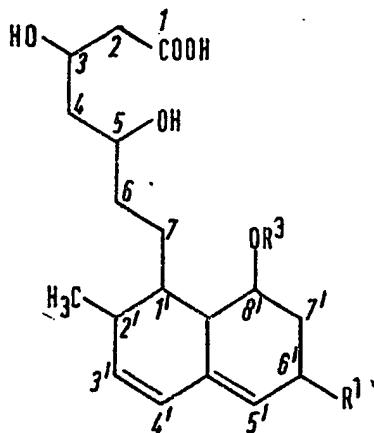


wherein:

R¹ represents a hydrogen atom or a methyl group;
 25 R² represents a hydrogen atom, the alcoholic moiety of an ester or the cationic moiety of a salt; R³, R⁴ and R⁵ are the same or different and each represents a hydrogen atom or an organic or inorganic acyl group, provided that, when R³ represents a 2-methylbutyryl group, R⁴ and R⁵ both represent acyl groups; and
 n is the valency of R².

30 The invention also provides processes for preparing the compounds of the invention by fermentation employing microorganisms of the genus *Penicillium* or *Monascus* or by hydrolysis, saponification or esterification reactions commencing with such fermentation products.

As the compounds of the invention are derivatives of the ML-236 and MB-530 group compounds in which the lactone ring has been broken, they are named as derivatives of ML-236 carboxylic acids or 35 MB-530 carboxylic acids (i.e. the carboxylic acids obtained by hydrolysis of ML-236 or MB-530 compounds) and the numbering system is that shown on the following structure:



(in which R¹ and R³ are as defined above).

In the compounds of formula (I), where R² represents the cationic moiety of a salt, it may be a metal atom, for example an alkali metal atom (e.g. sodium or potassium), an alkaline earth metal atom (e.g. calcium, magnesium or barium), a transition metal atom (e.g. iron, nickel or cobalt) or other metal atoms (e.g. aluminium, zinc or copper); in this case, n will be the well-known valency of these metals, in the examples given normally varying from 1 to 3. Alternatively, it may be an ammonium group or a substituted ammonium group (preferably an alkyl-substituted ammonium group), such as methylammonium, ethylammonium, isopropylammonium, dimethylammonium, diethylammonium, trimethylammonium, triethylammonium, tetramethylammonium, or dicyclohexylammonium; in this case, n will be 1. Another cationic moiety which may be represented by R² is the salt-forming group derived from a basic amino acid, such as lysine, arginine or ornithine.

Alternatively, R² may be the alcoholic moiety of an ester, in which case the value of n will depend upon the nature of the hydroxy compound from which R² is derived; for example in the case of mono-alcohols, n would be 1, in the case of glycols, n would be 2 and in the case of glycerol, n would be 3. Where R² represents a monovalent group, this is preferably an unsubstituted or substituted alkyl group, an unsubstituted or substituted aralkyl group or an unsubstituted or substituted phenacyl group.

Examples of alkyl groups which may be represented by R² include straight and branched chain alkyl groups, preferably having from 1 to 8 carbon atoms, for example the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, sec-pentyl, t-pentyl, isopentyl, neopentyl, hexyl, heptyl, 2-methylhexyl and octyl groups.

Examples of aralkyl groups which may be represented by R² include the benzyl group and the benzhydryl group, both of which may be unsubstituted or have one or more substituents in the benzene ring. Examples of such substituents include: C₁—C₄ alkyl groups (methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or t-butyl), C₁—C₄ alkoxy groups (methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy or t-butoxy), halogen atoms (e.g. chlorine, bromine or fluorine) or the trifluoromethyl group. Where there are two or more substituents, these may be the same or different. Examples of such aralkyl groups include the benzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-ethylbenzyl, 3-ethylbenzyl, 4-ethylbenzyl, 2-propylbenzyl, 3-propylbenzyl, 4-propylbenzyl, 2-butylbenzyl, 3-butylbenzyl, 4-butylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-propoxybenzyl, 3-propoxybenzyl, 4-propoxybenzyl, 2-butoxybenzyl, 3-butoxybenzyl, 4-butoxybenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl and benzhydryl groups.

Where R² represents a phenacyl group, this may be unsubstituted or may have one or more substituents in the benzene ring. Examples of such substituents include: C₁—C₄ alkyl groups, C₁—C₄ alkoxy groups, halogen atoms and the trifluoromethyl group; specific examples of these substituent groups are given above. Preferred examples of such phenacyl groups include the phenacyl, 2-methylphenacyl, 3-methylphenacyl, 4-methylphenacyl, 2-ethylphenacyl, 3-ethylphenacyl, 4-ethylphenacyl, 2-propylphenacyl, 3-propylphenacyl, 4-propylphenacyl, 2-butylphenacyl, 3-butylphenacyl, 4-butylphenacyl, 2-methoxyphenacyl, 3-methoxyphenacyl, 4-methoxyphenacyl, 2-ethoxyphenacyl, 3-ethoxyphenacyl, 4-ethoxyphenacyl, 2-propoxyphenacyl, 3-propoxyphenacyl, 4-propoxyphenacyl, 2-butoxyphenacyl, 3-butoxyphenacyl, 4-butoxyphenacyl, 2-chlorophenacyl, 3-chlorophenacyl, 4-chlorophenacyl, 2-bromophenacyl, 3-bromophenacyl, 4-bromophenacyl, 2-fluorophenacyl, 3-fluorophenacyl, 4-fluorophenacyl, 2-trifluoromethylphenacyl, 3-trifluoromethylphenacyl, 4-trifluoromethylphenacyl, and 2,6-difluorophenacyl groups.

Where R² represents a bivalent alcoholic moiety, it is preferably a C₂—C₆ alkylene or alkylidene group, for example an ethylene, ethylidene, propylene, propylidene, trimethylene, tetramethylene,

butylidene, pentamethylene or pentylidene group, as well as such groups having one or more substituents, e.g. hydroxy groups, halogen atoms or trifluoromethyl groups.

Where R² represents a trivalent alcoholic moiety, it is preferably a saturated aliphatic hydrocarbon group having from 2 to 6 carbon atoms and optionally one or more substituents, e.g. hydroxy groups,

5 halogen atoms or trifluoromethyl groups.

Where R³, R⁴ or R⁵ represents an acyl group, this may be an organic acyl group (for example an aliphatic acyl group, an aromatic acyl group, an araliphatic acyl group, an alicyclic acyl group, a heterocyclic acyl group, a heterocyclic-substituted aliphatic acyl group, an aliphatic sulphonyl group, an aromatic sulphonyl group, an aliphatic phosphoryl group, an aromatic phosphoryl group or an 10 araliphatic phosphoryl group) or an inorganic acyl group (for example an acyl group derived from phosphoric acid, sulphuric acid or nitric acid).

Where the acyl group is an aliphatic acyl group, this may be saturated or unsaturated and examples include: straight or branched chain C₂—C₂₀ alkanoyl groups (e.g. the acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, 2-methylvaleryl, heptanoyl, isoheptanoyl, 15 octanoyl, isoctanoyl, 2-methyloctanoyl, nonanoyl, isononanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, palmitoyl, stearoyl, isostearoyl, nonadecanoyl and eicosanoyl groups); C₃—C₂₀ alkenoyl groups (e.g. the acryloyl, crotonoyl, 3-butenoyl, methacryloyl, 3-methyl-2-butenoyl, 2-pentenoyl, 4-pentenoyl, tigloyl, angeloyl, 2-hexenoyl, 2-heptenoyl, hepta-2,4-dienoyl, 2-octenoyl, 2-nonenoyle, 2-decenoyl, 2-undecenoyl, linolenoyl, oleoyl, linoleoyl and 20 arachidonoyl groups); and C₃—C₂₀ alkynoyl groups (e.g. the propioloyl, 2-butynoyl, 3-butynoyl, 2-pentynoyl, 2-hexynoyl, 2-heptynoyl, 2-octynoyl, 2-nonynoyl and 2-decynoyl groups). These acyl groups

may be unsubstituted or may have one or more substituents, for example: halogen atoms, such as chlorine or bromine; the trifluoromethyl group; the nitro group; the carboxy group; alkoxy carbonyl groups, such as methoxycarbonyl or ethoxycarbonyl; aralkoxycarbonyl groups, such as 25 benzylloxycarbonyl; the cyano group; the amino group; alkanoylamino groups; such as acetyl amino; alkylamino groups, such as methylamino, dimethylamino or ethylamino; aralkylamino groups, such as benzylamino; the hydroxy group; alkanoyloxy groups, such as acetoxy or pivaloyloxy; alkoxy groups, such as methoxy or ethoxy; the sulphhydryl group; alkylthio groups, such as methylthio or ethylthio; and acylthio groups, such as acetylthio or benzylthio.

30 Where the acyl group represented by R³, R⁴ or R⁵ is an aromatic acyl group, the aromatic ring may be a single ring (e.g. a benzene ring) or a fused ring, for example a naphthalene ring, an anthracene ring or an indan ring. This ring may optionally have one or more substituents, for example alkyl groups, alkoxy groups, halogen atoms, trifluoromethyl groups, nitro groups, cyano groups, amino groups or hydroxy groups; where there are two or more substituents, these may be the same or different. Specific 35 examples of such aromatic acyl groups include the benzoyl, o-toluoyl, m-toluoyl, p-toluoyl, 2,4-dimethylbenzoyl, 3,4-dimethylbenzoyl, 2-ethylbenzoyl, 3-ethylbenzoyl, 4-ethylbenzoyl, 2-propylbenzoyl, 3-propylbenzoyl, 4-propylbenzoyl, 4-butylbenzoyl, o-anisoyl, m-anisoyl, p-anisoyl, 2,4-dimethoxybenzoyl, 2-ethoxybenzoyl, 3-ethoxybenzoyl, 4-ethoxybenzoyl, 2-propoxybenzoyl, 3-propoxybenzoyl, 4-propoxybenzoyl, 2-butoxybenzoyl, 3-butoxybenzoyl, 4-butoxybenzoyl, piperonyloyl, 40 dichlorobenzoyl, 3-chlorobenzoyl, 4-chlorobenzoyl, 2,3-dichlorobenzoyl, 3,4-dichlorobenzoyl, 2,4-dichlorobenzoyl, 2-bromobenzoyl, 3-bromobenzoyl, 4-bromobenzoyl, 2-fluorobenzoyl, 3-fluorobenzoyl, 2,4-fluorobenzoyl, 2-trifluoromethylbenzoyl, 3-trifluoromethylbenzoyl, 4-trifluoromethylbenzoyl, 2-nitrobenzoyl, 3-nitrobenzoyl, 4-nitrobenzoyl, 2,4-dinitrobenzoyl, 3,5-dinitrobenzoyl, salicyloyl, 3-hydroxybenzoyl, 4-hydroxybenzoyl, 2-acetoxybenzoyl, 3-acetoxybenzoyl, 4-acetoxybenzoyl, 45 antraniloyl, 2-acetamidobenzoyl, 4-acetamidobenzoyl, vanillyl, veratroyl, protocatechuyl, galloyl, 1-naphthoyl, 2-naphthoyl, 2-antranoyl, 4-indanecarbonyl, 5-indanecarbonyl and 4-indenecarbonyl groups.

Where the acyl group represented by R³, R⁴ or R⁵ is an araliphatic acyl group, the aromatic ring in this araliphatic acyl group may be a single ring or a fused ring, as exemplified above for the aromatic 50 acyl group, whilst the aliphatic moiety may be saturated or unsaturated. The aromatic ring may optionally have one or more substituents, as exemplified above for the aromatic acyl groups. Examples of such araliphatic acyl groups include the phenylacetyl, 2-methylphenylacetyl, 3-methylphenylacetyl, 4-methylphenylacetyl, 2-ethylphenylacetyl, 2-methoxyphenylacetyl, 3-methoxyphenylacetyl, 4-methoxyphenylacetyl, 2-ethoxyphenylacetyl, 3-ethoxyphenylacetyl, 4-ethoxyphenylacetyl, 2-propoxyphenylacetyl, 3-propoxyphenylacetyl, 4-propoxyphenylacetyl, 2,4-dimethoxyphenylacetyl, 3,4-methylenedioxyphe-

nacyl, 2-hydroxyphenylacetyl, 3-hydroxyphenylacetyl, 4-hydroxyphenylacetyl, 2,4-dichlorophenylacetyl, 2,4-dichlorophenylacetyl, 3,5-dichlorophenylacetyl, 2-bromophenylacetyl, 3-bromophenylacetyl, 4-bromophenylacetyl, 2-nitrophenylacetyl, 3-nitrophenylacetyl, 4-nitrophenylacetyl, 4-aminophenyl-

60 acetyl, 2-phenylpropionyl, 3-(2-methylphenyl)propionyl, 3-(3-methylphenyl)propionyl, 3-(4-methoxyphenyl)propionyl, 3-(2-methoxyphenyl)propionyl, 3-(3-methoxyphenyl)propionyl, 3-(4-methoxyphenyl)propionyl, 3-(3,4-methylenedioxyphe-

nacyl)propionyl, 3-(4-chlorophenyl)propionyl, phenoxyacetyl, cinnamoyl, o-methylcinnamoyl, p-methylcinnamoyl, p-methylcinnamoyl, o-methoxycinnamoyl, m-methoxycinnamoyl, p-methoxycinnamoyl, o-hydroxycinnamoyl, m-hydroxycinnamoyl, p-hydroxycinnamoyl, o-

65 methoxycinnamoyl, o-hydroxycinnamoyl, m-hydroxycinnamoyl, p-hydroxycinnamoyl, o-

chlorocinnamoyl, *m*-chlorocinnamoyl, *p*-chlorocinnamoyl, *o*-bromocinnamoyl, *m*-bromocinnamoyl and *p*-bromocinnamoyl groups.

Where the acyl group represented by R³, R⁴, or R⁵ is an alicyclic acyl group, the alicyclic ring may be saturated or unsaturated and preferably has from 3 to 7 carbon atoms. Examples of such alicyclic

5 acyl groups include the cyclopropanecarbonyl, cyclobutanecarbonyl, cyclobut-1-enecarbonyl, cyclobut-5
2-enecarbonyl, cyclo-pentanecarbonyl, cyclopent-1-enecarbonyl, cyclopent-2-enecarbonyl,

10 cyclopenta-1,3-dienecarbonyl, cyclopenta-2,4-dienecarbonyl, cyclohexanecarbonyl, cyclohex-1-ene-5
carbonyl, cyclohex-2-enecarbonyl, cyclohex-3-enecarbonyl, cyclohexa-1,3-dienecarbonyl, cyclohexa-10
2,4-dienecarbonyl, cycloheptanecarbonyl, cyclohept-1-enecarbonyl, cyclohept-2-enecarbonyl,

15 cyclohept-3-enecarbonyl, cyclohepta-1,3-dienecarbonyl, cyclohepta-2,4-dienecarbonyl, cyclohepta-5
2,5-dienecarbonyl, cyclohepta-1,4-dienecarbonyl, cyclohepta-1,5-dienecarbonyl, cyclohepta-1,3,5-10
triencarbonyl, cyclohepta-2,4,6-trienecarbonyl and adamantanecarbonyl groups. These rings may
optionally have one or more substituents, as exemplified above in respect of the aromatic acyl groups
and such substituents may form one or more rings fused to the abovementioned alicyclic ring system.

15 Where the acyl group represented by R³, R⁴ or R⁵ is a heterocyclic acyl group, the heterocyclic 15
ring preferably has 5 or 6 ring atoms, one or more of which is a hetero atom, for example a nitrogen
atom, an oxygen atom, a sulphur atom or a selenium atom. This heterocyclic ring may optionally be
fused with a carbocyclic ring or with another heterocyclic ring (which may be the same as or different
from the first-mentioned heterocyclic ring) to form a fused heterocyclic ring system. The heterocyclic

20 acyl group may have one or more substituents, as exemplified above in respect of the aromatic acyl 20
groups. Specific examples of such heterocyclic acyl groups include the 2-thenoyl, 3-thenoyl, 5-
methylthen-2-oyl, 5-chlorothen-2-oyl, 4,5-dimethylthen-3-oyl, 2-furoyl, 3-furoyl, 5-methylfur-2-oyl, 5-
chlorfur-2-oyl, pyridine-2-carbonyl, 3-methylpyridine-2-carbonyl, 4-methylpyridine-2-carbonyl, 5-
methylpyridine-2-carbonyl, 6-methyl-pyridine-2-carbonyl, nicotinoyl, isonicotinoyl, isoxazole-3-
25 carbonyl, isoxazole-4-carbonyl, oxazole-2-carbonyl, oxazole-4-carbonyl, 4-acetylaminothiazole-2-
carbonyl, 1,3,4-thiadiazole-2-carbonyl, 5-methyl-1,3,4-thiadiazole-2-carbonyl, 1,2,3-triazole-1-
carbonyl, 1,2,3,4-tetrazole-1-carbonyl, piperidinecarbonyl, 4-methyl-1-piperazine-carbonyl, 1-
pyrrolidinecarbonyl, benzofuran-2-carbonyl and benzothiophene-2-carbonyl groups.

30 Where the acyl group represented by R³, R⁴ or R⁵ is a heterocyclic-substituted aliphatic acyl 30
group, the heterocyclic group may be as described above for the heterocyclic acyl groups and the
aliphatic moiety may be saturated or unsaturated and may be as described above for aliphatic acyl
groups. Examples of such heterocyclic-substituted aliphatic acyl groups include the 2-thienylacetyl, (5-
methylthiophene-2-yl)acetyl, (5-chlorothiophene-2-yl)acetyl, 3-thienylacetyl, 2-furylacetyl, 3-
furylacetyl, 2-pyridylacetyl, 3-pyridylacetyl, 4-pyridylacetyl, 2-furylacyroyl, 3-furylacyroyl, 2-
35 thienylacryloyl, 3-thienylacryloyl, piperidinoacetyl and 4-methylpiperidinoacetyl, 2-amino-3-(indol-2-
yl)propionyl and 2-amino-3-(indol-3-yl)propionyl groups.

40 Where the acyl group represented by R³, R⁴ or R⁵ is a sulphonyl group, this may be an aliphatic 40
sulphonyl group (for example a methanesulphonyl or ethanesulphonyl group) or an aromatic sulphonyl
group (e.g. a benzene-sulphonyl or toluenesulphonyl group).

45 Where the acyl group represented by R³, R⁴ or R⁵ is a phosphoryl group, this may be an aliphatic 45
phosphoryl group (e.g. a dimethylphosphoryl or diethylphosphoryl group), an aromatic phosphoryl
group (e.g. a ditolylphosphoryl group) or an araliphatic phosphoryl group (e.g. a dibenzylphosphoryl, *p*-
m-methylbenzylphosphoryl, *p*-bromobenzylphosphoryl or *p*-methoxybenzylphosphoryl group).

50 Of the compounds of the invention, those compounds are preferred where:

45 R¹ represents a hydrogen atom or a methyl group;

R² represents a hydrogen atom, a metal atom (particularly an alkali metal atom, an alkaline earth metal atom or an aluminium, zinc, iron or germanium atom), an ammonium group, an alkyl-substituted ammonium group, a group capable of forming a salt derived from a basic amino acid, an alkyl group (preferably a straight or branched chain C₁—C₈ alkyl group), an aralkyl group optionally having one or 50
more substituents on the aryl moiety or a phenacyl group optionally having one or more substituents on the phenyl moiety, those substituents being selected from C₁—C₄ alkyl groups, C₁—C₄ alkoxy groups, halogen atoms and trifluoromethyl groups; and

55 R³, R⁴ and R⁵ are the same or different and each represents a hydrogen atom, an aliphatic acyl group (preferably a C₂—C₂₀ alkanoyl group, a C₃—C₂₀ alkenoyl group or a C₃—C₂₀ alkynoyl group), an aromatic acyl group (preferably a C₇—C₁₆ group) or an araliphatic acyl group (preferably a C₈ or C₉ aralkanoyl group or a C₈ aralkenoyl group) provided that, when R³ represents a 2-methylbutyryl group, R⁴ and R⁵ both represent acyl groups.

60 More preferred compounds of formula (I) are those in which:
R¹ represents a hydrogen atom or a methyl group;
R² represents a hydrogen atom, an alkali metal atom, an alkaline earth metal atom, an ammonium group, a group capable of forming a salt derived from a basic amino acid, a C₁—C₄ alkyl group, a benzyl group or a phenacyl group; and
65 R³, R⁴ and R⁵ are the same or different and each represents a hydrogen atom, a C₂—C₈ alkanoyl group, a C₃—C₈ alkenoyl group or a benzoyl group, provided that, when R³ represents a 2-methylbutyryl group, both R⁴ and R⁵ represent acyl groups.

The most preferred compounds are those in which:

R¹ represents a hydrogen atom or a methyl group (particularly a hydrogen atom);

R² represents a C₁—C₄ alkyl group, a benzyl group or a phenacyl group (particularly a C₁—C₄ alkyl group);

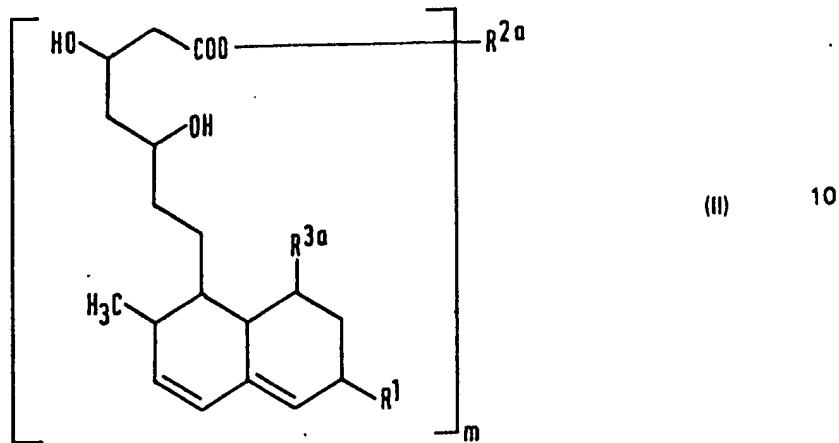
5 R³ represents a C₂—C₆ alkanoyl group or a C₃—C₆ alkenoyl group (particularly a C₂—C₆ alkanoyl group); and

R⁴ and R⁵ are the same or different and each represents a C₂—C₆ alkanoyl group or a benzoyl group (particularly an acetyl group or a benzoyl group).

5 One useful class of compounds of the present invention are those compounds of formula (II):

10

10



in which:

R¹ represents a hydrogen atom or a methyl group;

R^{2a} represents a hydrogen atom, an alkali metal atom, an alkaline earth metal atom, an ammonium group, a group capable of forming a salt derived from a basic amino acid, a C₁—C₄ alkyl group, a benzyl group or a phenacyl group;

15 R^{3a} represents a C₂—C₆ alkanoyl group (other than a 2-methylbutyryl group) or a C₃—C₆ alkenoyl group; and

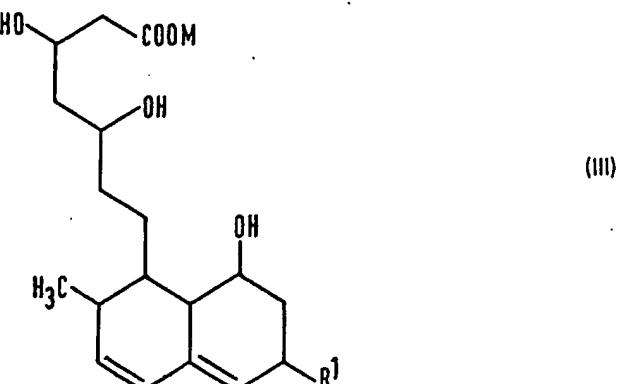
m is the valence of the atom or group represented by R^{2a}.

Particularly preferred are those compounds of formula (II) in which R^{2a} represents a C₁—C₄ alkyl group, a benzyl group or a phenacyl group and those compounds of formula (II) in which R^{2a} represents an alkali metal atom.

Another particularly useful class of compounds of the present invention are those compounds of formula (III):

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25 in which:

R¹ represents a hydrogen atom or methyl group; and

M represents a hydrogen atom or an alkali metal atom, particularly an alkali metal atom and preferably a sodium atom.

Examples of compounds of the invention are given in the following list, in which, as explained above, the compounds are named as derivatives of ML-236A, ML-236B, MB-530A or MB-530B or their corresponding carboxylic acids:

30 1. Sodium ML-236A-carboxylate

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30

	2. Calcium bis(ML-236A-carboxylate)	
	3. Sodium MB-530A-carboxylate	
	4. Calcium bis(MB-530A-carboxylate)	
5	5. Methyl ML-236A-carboxylate	5
	6. Ethyl ML-236A-carboxylate	
	7. Butyl ML-236A-carboxylate	
	8. Benzyl ML-236A-carboxylate	
	9. <i>p</i> -Bromobenzyl ML-236A-carboxylate	
10	10. <i>p</i> -Methoxybenzyl ML-236A-carboxylate	10
	11. Phenacyl ML-236A-carboxylate	
	12. <i>p</i> -Methoxyphenacyl ML-236A-carboxylate	
	13. Methyl MB-530A-carboxylate	
	14. Ethyl MB-530A-carboxylate	
15	15. Butyl MB-530A-carboxylate	15
	16. Benzyl MB-530A-carboxylate	
	17. <i>p</i> -Methoxybenzyl-MB-530A-carboxylate	
	18. Phenacyl MB-530A-carboxylate	
	19. <i>p</i> -Methoxyphenacyl MB-530A-carboxylate	
20	20. Sodium 8'-O-acetyl-ML-236A-carboxylate	20
	21. Methyl 8'-O-acetyl-ML-236A-carboxylate	
	22. Ethyl 8'-O-acetyl-ML-236A-carboxylate	
	23. Butyl 8'-O-acetyl-ML-236A-carboxylate	
	24. Benzyl 8'-O-acetyl-ML-236A-carboxylate	
25	25. <i>p</i> -Methoxybenzyl 8'-O-acetyl-ML-236A-carboxylate	25
	26. Phenacyl 8'-O-acetyl-ML-236A-carboxylate	
	27. <i>p</i> -Methoxyphenacyl 8'-O-acetyl-ML-236A-carboxylate	
	28. Sodium 8'-O-acetyl-MB-530A-carboxylate	
	29. Methyl 8'-O-acetyl-MB-530A-carboxylate	
	30. Ethyl 8'-O-acetyl-MB-530A-carboxylate	
30	31. Butyl 8'-O-acetyl-MB-530A-carboxylate	30
	32. Benzyl 8'-O-acetyl-MB-530A-carboxylate	
	33. <i>p</i> -Methoxybenzyl 8'-O-acetyl-MB-530A-carboxylate	
	34. Phenacyl 8'-O-acetyl-MB-530A-carboxylate	
	35. <i>p</i> -Methoxyphenacyl 8'-O-acetyl-MB-530A-carboxylate	
35	36. Sodium 8'-O-propionyl-ML-236A-carboxylate	35
	37. Methyl 8'-O-propionyl-ML-236A-carboxylate	
	38. Ethyl 8'-O-propionyl-ML-236A-carboxylate	
	39. Benzyl 8'-O-propionyl-ML-236A-carboxylate	
	40. Phenacyl 8'-O-propionyl-ML-236A-carboxylate	
40	41. Sodium 8'-O-propionyl-MB-530A-carboxylate	40
	42. Methyl 8'-O-propionyl-MB-530A-carboxylate	
	43. Ethyl 8'-O-propionyl-MB-530A-carboxylate	
	44. Butyl 8'-O-propionyl-MB-530A-carboxylate	
	45. Benzyl 8'-O-propionyl-MB-530A-carboxylate	
45	46. Phenacyl 8'-O-propionyl-MB-530A-carboxylate	45
	47. Sodium 8'-O-butyryl-ML-236A-carboxylate	
	48. Magnesium bis(8'-O-butyryl-ML-236A-carboxylate)	
	49. Aluminium tris(8'-O-butyryl-ML-236A-carboxylate)	
	50. Methyl 8'-O-butyryl-ML-236A-carboxylate	
50	51. Ethyl 8'-O-butyryl-ML-236A-carboxylate	50
	52. Butyl 8'-O-butyryl-ML-236A-carboxylate	
	53. Benzyl 8'-O-butyryl-ML-236A-carboxylate	
	54. Phenacyl 8'-O-butyryl-ML-236A-carboxylate	
	55. Dimethylaminoethyl 8'-O-butyryl-ML-236A-carboxylate	
55	56. Sodium 8'-O-butyryl-MB-530A-carboxylate	55
	57. Calcium bis(8'-O-butyryl-MB-530A-carboxylate)	
	58. Methyl 8'-O-butyryl-MB-530A-carboxylate	
	59. Ethyl 8'-O-butyryl-MB-530A-carboxylate	
	60. Butyl 8'-O-butyryl-MB-530A-carboxylate	
60	61. Benzyl 8'-O-butyryl-MB-530A-carboxylate	60
	62. Phenacyl 8'-O-butyryl-MB-530A-carboxylate	
	63. Sodium 8'-O-(4-pentenoyl)-ML-236A-carboxylate	
	64. Methyl 8'-O-(4-pentenoyl)-ML-236A-carboxylate	
	65. Ethyl 8'-O-(4-pentenoyl)-ML-236A-carboxylate	
65	66. Butyl 8'-O-(4-pentenoyl)-ML-236A-carboxylate	65

	67. Benzyl 8'-O-(4-pentenoyl)-ML-236A-carboxylate	
	68. Phenacyl 8'-O-(4-pentenoyl)-ML-236A-carboxylate	
	69. Sodium 8'-O-(4-pentenoyl)-MB-530A-carboxylate	
5	70. Methyl 8'-O-(4-pentenoyl)-MB-530A-carboxylate	5
	71. Ethyl 8'-O-(4-pentenoyl)-MB-530A-carboxylate	
	72. Butyl 8'-O-(4-pentenoyl)-MB-530A-carboxylate	
	73. Benzyl 8'-O-(4-pentenoyl)-MB-530A-carboxylate	
	74. Phenacyl 8'-O-(4-pentenoyl)-MB-530A-carboxylate	
10	75. Sodium 8'-O-isovaleryl-ML-236A-carboxylate	10
	76. Methyl 8'-O-isovaleryl-ML-236A-carboxylate	
	77. Ethyl 8'-O-isovaleryl-ML-236A-carboxylate	
	78. Butyl 8'-O-isovaleryl-ML-236A-carboxylate	
	79. Benzyl 8'-O-isovaleryl-ML-236A-carboxylate	
15	80. Phenacyl 8'-O-isovaleryl-ML-236A-carboxylate	1.5
	81. Sodium 8'-O-isovaleryl-MB-530A-carboxylate	
	82. Methyl 8'-O-isovaleryl-MB-530A-carboxylate	
	83. Ethyl 8'-O-isovaleryl-MB-530A-carboxylate	
	84. Butyl 8'-O-isovaleryl-MB-530A-carboxylate	
20	85. Benzyl 8'-O-isovaleryl-MB-530A-carboxylate	20
	86. Phenacyl 8'-O-isovaleryl-MB-530A-carboxylate	
	87. Sodium 8'-O-hexanoyl-ML-236A-carboxylate	
	88. Methyl 8'-O-hexanoyl-ML-236A-carboxylate	
	89. Ethyl 8'-O-hexanoyl-ML-236A-carboxylate	
25	90. Butyl 8'-O-hexanoyl-ML-236A-carboxylate	25
	91. Benzyl 8'-O-hexanoyl-ML-236A-carboxylate	
	92. Phenacyl 8'-O-hexanoyl-ML-236A-carboxylate	
	93. Sodium 8'-O-hexanoyl-MB-530A-carboxylate	
	94. Methyl 8'-O-hexanoyl-MB-530A-carboxylate	
30	95. Ethyl 8'-O-hexanoyl-MB-530A-carboxylate	30
	96. Butyl 8'-O-hexanoyl-MB-530A-carboxylate	
	97. Benzyl 8'-O-hexanoyl-MB-530A-carboxylate	
	98. Phenacyl 8'-O-hexanoyl-MB-530A-carboxylate	
	99. Sodium 8'-O-palmitoyl-ML-236A-carboxylate	
35	100. Methyl 8'-O-palmitoyl-ML-236A-carboxylate	35
	101. Benzyl 8'-O-palmitoyl-ML-236A-carboxylate	
	102. Phenacyl 8'-O-palmitoyl-ML-236A-carboxylate	
	103. Sodium 8'-O-palmitoyl-MB-530A-carboxylate	
	104. Methyl 8'-O-palmitoyl-MB-530A-carboxylate	
40	105. Ethyl 8'-O-palmitoyl-MB-530A-carboxylate	40
	106. Benzyl 8'-O-palmitoyl-MB-530A-carboxylate	
	107. Sodium 8'-O-stearoyl-ML-236A-carboxylate	
	108. Sodium 8'-O-stearoyl-MB-530A-carboxylate	
	109. Sodium 8'-O-linolenoyl-ML-236A-carboxylate	
45	110. Methyl 8'-O-linolenoyl-ML-236A-carboxylate	45
	111. Sodium 8'-O-linolenoyl-MB-530A-carboxylate	
	112. Methyl 8'-O-linolenoyl-MB-530A-carboxylate	
	113. Sodium 8'-O-benzoyl-ML-236A-carboxylate	
	114. Potassium 8'-O-benzoyl-ML-236A-carboxylate	
50	115. Aluminum tris(8'-O-benzoyl-ML-236A-carboxylate)	50
	116. Methyl 8'-O-benzoyl-ML-236A-carboxylate	
	117. Ethyl 8'-O-benzoyl-ML-236A-carboxylate	
	118. Butyl 8'-O-benzoyl-ML-236A-carboxylate	
	119. Benzyl 8'-O-benzoyl-ML-236A-carboxylate	
	120. p-Methoxybenzyl 8'-O-benzoyl-ML-236A-carboxylate	
55	121. Phenacyl 8'-O-benzoyl-ML-236A-carboxylate	55
	122. p-Methoxyphenacyl 8'-O-benzoyl-ML-236A-carboxylate	
	123. Sodium 8'-O-benzoyl-MB-530A-carboxylate	
	124. Potassium 8'-O-benzoyl-MB-530A-carboxylate	
	125. Aluminum tris(8'-O-benzoyl-MB-530A-carboxylate)	
60	126. Methyl 8'-O-benzoyl-MB-530A-carboxylate	60
	127. Ethyl 8'-O-benzoyl-MB-530A-carboxylate	
	128. Butyl 8'-O-benzoyl-MB-530A-carboxylate	
	129. Benzyl 8'-O-benzoyl-MB-530A-carboxylate	
	130. p-Methoxybenzyl 8'-O-benzoyl-MB-530A-carboxylate	
65	131. Phenacyl 8'-O-benzoyl-MB-530A-carboxylate	65

	132. <i>p</i> -Methoxyphenacyl 8'-O-benzoyl-MB-530A-carboxylate	
	133. Sodium 8'-O-(<i>p</i> -toluoyl)-ML-236A-carboxylate	
	134. Calcium bis[8'-O-(<i>p</i> -toluoyl)-ML-236A-carboxylate]	
	135. Ethyl 8'-O-(<i>p</i> -toluoyl)-ML-236A-carboxylate	
5	136. Butyl 8'-O-(<i>p</i> -toluoyl)-ML-236A-carboxylate	5
	137. Benzyl 8'-O-(<i>p</i> -toluoyl)-ML-236A-carboxylate	
	138. Phenacyl 8'-O-(<i>p</i> -toluoyl)-ML-236A-carboxylate	
	139. Sodium 8'-O-(<i>p</i> -toluoyl)-MB-530A-carboxylate	
10	140. Methyl 8'-O-(<i>p</i> -toluoyl)-MB-530A-carboxylate	10
	141. Butyl 8'-O-(<i>p</i> -toluoyl)-MB-530A-carboxylate	
	142. Benzyl 8'-O-(<i>p</i> -toluoyl)-MB-530A-carboxylate	
	143. Phenacyl 8'-O-(<i>p</i> -toluoyl)-MB-530A-carboxylate	
	144. Sodium 8'-O-(2-chlorobenzoyl)-ML-236A-carboxylate	
15	145. Sodium 8'-O-(2-chlorobenzoyl)-MB-530A-carboxylate	15
	146. Sodium 8'-O-(3-chlorobenzoyl)-ML-236A-carboxylate	
	147. Sodium 8'-O-(3-chlorobenzoyl)-MB-530A-carboxylate	
	148. Sodium 8'-O-(4-chlorobenzoyl)-ML-236A-carboxylate	
	149. Sodium 8'-O-(4-chlorobenzoyl)-MB-530A-carboxylate	
	150. Sodium 8'-O-salicyloyl-ML-236A-carboxylate	
20	151. Potassium 8'-O-salicyloyl-ML-236A-carboxylate	20
	152. Methyl 8'-O-salicyloyl-ML-236A-carboxylate	
	153. Ethyl 8'-O-salicyloyl-ML-236A-carboxylate	
	154. Butyl 8'-O-salicyloyl-ML-236A-carboxylate	
	155. Benzyl 8'-O-salicyloyl-ML-236A-carboxylate	
25	156. Phenacyl 8'-O-salicyloyl-ML-236A-carboxylate	25
	157. Sodium 8'-O-salicyloyl-MB-530A-carboxylate	
	158. Potassium 8'-O-salicyloyl-MB-530A-carboxylate	
	159. Methyl 8'-O-salicyloyl-MB-530A-carboxylate	
	160. Ethyl 8'-O-salicyloyl-MB-530A-carboxylate	
30	161. Butyl 8'-O-salicyloyl-MB-530A-carboxylate	30
	162. Benzyl 8'-O-salicyloyl-MB-530A-carboxylate	
	163. Phenacyl 8'-O-salicyloyl-MB-530A-carboxylate	
	164. Sodium 8'-O-phenylacetyl-ML-236A-carboxylate	
	165. Methyl 8'-O-phenylacetyl-ML-236A-carboxylate	
35	166. Ethyl 8'-O-phenylacetyl-ML-236A-carboxylate	35
	167. Benzyl 8'-O-phenylacetyl-ML-236A-carboxylate	
	168. Sodium 8'-O-phenylacetyl-MB-530A-carboxylate	
	169. Methyl 8'-O-phenylacetyl-MB-530A-carboxylate	
	170. Ethyl 8'-O-phenylacetyl-MB-530A-carboxylate	
40	171. Benzyl 8'-O-phenylacetyl-MB-530A-carboxylate	40
	172. Sodium 8'-O-cinnamoyl-ML-236A-carboxylate	
	173. Sodium 8'-O-cinnamoyl-MB-530A-carboxylate	
	174. Sodium 8'-O-(<i>p</i> -hydroxycinnamoyl)-ML-236A-carboxylate	
45	175. Sodium 8'-O-(<i>p</i> -hydroxycinnamoyl)-MB-530A-carboxylate	45
	176. Sodium 8'-O-cyclohexanecarbonyl-ML-236A-carboxylate	
	177. Sodium 8'-O-cyclohexanecarbonyl-MB-530A-carboxylate	
	178. Sodium 8'-O-(2-thenoyl)-ML-236A-carboxylate	
	179. Methyl 8'-O-(2-thenoyl)-ML-236A-carboxylate	
	180. Ethyl 8'-O-(2-thenoyl)-ML-236A-carboxylate	
50	181. Sodium 8'-O-(2-thenoyl)-MB-530A-carboxylate	50
	182. Methyl 8'-O-(2-thenoyl)-MB-530A-carboxylate	
	183. Ethyl 8'-O-(2-thenoyl)-MB-530A-carboxylate	
	184. Sodium 8'-O-(2-furoyl)-ML-236A-carboxylate	
	185. Methyl 8'-O-(2-furoyl)-ML-236A-carboxylate	
55	186. Ethyl 8'-O-(2-furoyl)-ML-236A-carboxylate	55
	187. Sodium 8'-O-(2-furoyl)-MB-530A-carboxylate	
	188. Methyl 8'-O-(2-furoyl)-MB-530A-carboxylate	
	189. Ethyl 8'-O-(2-furoyl)-MB-530A-carboxylate	
	190. Sodium 8'-O-(2-thienylacetyl)-ML-236A-carboxylate	
60	191. Methyl 8'-O-(2-thienylacetyl)-ML-236A-carboxylate	60
	192. Ethyl 8'-O-(2-thienylacetyl)-ML-236A-carboxylate	
	193. Butyl 8'-O-(2-thienylacetyl)-ML-236A-carboxylate	
	194. Benzyl 8'-O-(2-thienylacetyl)-ML-236A-carboxylate	
65	195. Phenacyl 8'-O-(2-thienylacetyl)-ML-236A-carboxylate	65
	196. Sodium 8'-O-(2-thienylacetyl)-MB-530A-carboxylate	

	197. Methyl 8'-O-(2-thienylacetyl)-MB-530A-carboxylate	
	198. Ethyl 8'-O-(2-thienylacetyl)-MB-530A-carboxylate	
	199. Sodium 8'-O-methanesulphonyl-ML-236A-carboxylate	
5	200. Methyl 8'-O-methanesulphonyl-ML-236A-carboxylate	5
	201. Ethyl 8'-O-methanesulphonyl-ML-236A-carboxylate	
	202. Sodium 8'-O-methanesulphonyl-ML-236A-carboxylate	
	203. Methyl 8'-O-methanesulphonyl-ML-236A-carboxylate	
	204. Ethyl 8'-O-methanesulphonyl-ML-236A-carboxylate	
10	205. Trisodium 8'-O-phosphoryl-ML-236A-carboxylate	10
	206. Trisodium 8'-O-phosphoryl-ML-236A-carboxylate	
	207. Sodium 3-O-acetyl-ML-236A-carboxylate	
	208. Methyl 3-O-acetyl-ML-236A-carboxylate	
	209. Ethyl 3-O-acetyl-ML-236A-carboxylate	
15	210. Butyl 3-O-acetyl-ML-236A-carboxylate	15
	211. Benzyl 3-O-acetyl-ML-236A-carboxylate	
	212. Sodium 3-O-acetyl-ML-236A-carboxylate	
	213. Methyl 3-O-acetyl-ML-236A-carboxylate	
	214. Butyl 3-O-acetyl-ML-236A-carboxylate	
20	215. Benzyl 3-O-acetyl-ML-236A-carboxylate	20
	216. Sodium 3-O-butyryl-ML-236A-carboxylate	
	217. Methyl 3-O-butyryl-ML-236A-carboxylate	
	218. Butyl 3-O-butyryl-ML-236A-carboxylate	
	219. Benzyl 3-O-butyryl-ML-236A-carboxylate	
25	220. Sodium 3-O-butyryl-ML-236A-carboxylate	25
	221. Methyl 3-O-butyryl-ML-236A-carboxylate	
	222. Ethyl 3-O-butyryl-ML-236A-carboxylate	
	223. Benzyl 3-O-butyryl-ML-236A-carboxylate	
	224. Sodium 3-O-benzoyl-ML-236A-carboxylate	
30	225. Methyl 3-O-benzoyl-ML-236A-carboxylate	30
	226. Ethyl 3-O-benzoyl-ML-236A-carboxylate	
	227. Butyl 3-O-benzoyl-ML-236A-carboxylate	
	228. Benzyl 3-O-benzoyl-ML-236A-carboxylate	
	229. Sodium 3-O-benzoyl-ML-236A-carboxylate	
35	230. Methyl 3-O-benzoyl-ML-236A-carboxylate	35
	231. Ethyl 3-O-benzoyl-ML-236A-carboxylate	
	232. Butyl 3-O-benzoyl-ML-236A-carboxylate	
	233. Benzyl 3-O-benzoyl-ML-236A-carboxylate	
	234. Sodium 3,8'-di(O-acetyl)-ML-236A-carboxylate	
40	235. Methyl 3,8'-di(O-acetyl)-ML-236A-carboxylate	40
	236. Ethyl 3,8'-di(O-acetyl)-ML-236A-carboxylate	
	237. Benzyl 3,8'-di(O-acetyl)-ML-236A-carboxylate	
	238. Sodium 3,8'-di(O-acetyl)-ML-236A-carboxylate	
	239. Methyl 3,8'-di(O-acetyl)-ML-236A-carboxylate	
	240. Butyl 3,8'-di(O-acetyl)-ML-236A-carboxylate	
45	241. Benzyl 3,8'-di(O-acetyl)-ML-236A-carboxylate	45
	242. Sodium 3,8'-di(O-butyryl)-ML-236A-carboxylate	
	243. Methyl 3,8'-di(O-butyryl)-ML-236A-carboxylate	
	244. Butyl 3,8'-di(O-butyryl)-ML-236A-carboxylate	
	245. Benzyl 3,8'-di(O-butyryl)-ML-236A-carboxylate	
50	246. Sodium 3,8'-di(O-butyryl)-ML-236A-carboxylate	50
	247. Methyl 3,8'-di(O-butyryl)-ML-236A-carboxylate	
	248. Butyl 3,8'-di(O-butyryl)-ML-236A-carboxylate	
	249. Benzyl 3,8'-di(O-butyryl)-ML-236A-carboxylate	
	250. Sodium 3,8'-di(O-benzoyl)-ML-236A-carboxylate	
55	251. Methyl 3,8'-di(O-benzoyl)-ML-236A-carboxylate	55
	252. Ethyl 3,8'-di(O-benzoyl)-ML-236A-carboxylate	
	253. Butyl 3,8'-di(O-benzoyl)-ML-236A-carboxylate	
	254. Benzyl 3,8'-di(O-benzoyl)-ML-236A-carboxylate	
	255. Sodium 3,8'-di(O-benzoyl)-ML-236A-carboxylate	
60	256. Methyl 3,8'-di(O-benzoyl)-ML-236A-carboxylate	60
	257. Butyl 3,8'-di(O-benzoyl)-ML-236A-carboxylate	
	258. Benzyl 3,8'-di(O-benzoyl)-ML-236A-carboxylate	
	259. Sodium 3-O-acetyl-8'-O-butyryl-ML-236A-carboxylate	
	260. Sodium 3-O-acetyl-8'-O-butyryl-ML-236A-carboxylate	
65	261. Sodium 3-O-butyryl-8'-O-acetyl-ML-236A-carboxylate	65

	262. Sodium 3-O-butyryl-8'-O-acetyl-MB-530A-carboxylate	
	263. Sodium 3-O-benzoyl-8'-O-acetyl-ML-236A-carboxylate	
	264. Sodium 3-O-benzoyl-8'-O-acetyl-MB-530A-carboxylate	
	265. Sodium 3-O-benzoyl-8'-O-butyryl-ML-236A-carboxylate	
5	266. Sodium 3-O-benzoyl-8'-O-butyryl-MB-530A-carboxylate	5
	267. Sodium 3-O-acetyl-8'-O-benzoyl-ML-236A-carboxylate	
	268. Sodium 3-O-acetyl-8'-O-benzoyl-MB-530A-carboxylate	
	269. Sodium 3-O-butyryl-8'-O-benzoyl-ML-236A-carboxylate	
	270. Sodium 3-O-butyryl-8'-O-benzoyl-MB-530A-carboxylate	
10	271. Sodium 3,5,8'-tri(O-acetyl)-ML-236A-carboxylate	10
	272. Potassium 3,5,8'-tri(O-acetyl)-ML-236A-carboxylate	
	273. Methyl 3,5,8'-tri(O-acetyl)-ML-236A-carboxylate	
	274. Ethyl 3,5,8'-tri(O-acetyl)-ML-236A-carboxylate	
15	275. Butyl 3,5,8'-tri(O-acetyl)-ML-236A-carboxylate	15
	276. Benzyl 3,5,8'-tri(O-acetyl)-ML-236A-carboxylate	
	277. Phenacyl 3,5,8'-tri(O-acetyl)-ML-236A-carboxylate	
	278. Sodium 3,5,8'-tri(O-butyryl)-ML-236A-carboxylate	
	279. Methyl 3,5,8'-tri(O-butyryl)-ML-236A-carboxylate	
20	280. Ethyl 3,5,8'-tri(O-butyryl)-ML-236A-carboxylate	20
	281. Butyl 3,5,8'-tri(O-butyryl)-ML-236A-carboxylate	
	282. Benzyl 3,5,8'-tri(O-butyryl)-ML-236A-carboxylate	
	283. Pivaloyloxymethyl 3,5,8'-tri(O-butyryl)-ML-236A-carboxylate	
	284. Phenacyl 3,5,8'-tri(O-butyryl)-ML-236A-carboxylate	
	285. Sodium 3,5,8'-tri(O-butyryl)-MB-530A-carboxylate	
25	286. Potassium 3,5,8'-tri(O-butyryl)-MB-530A-carboxylate	25
	287. Methyl 3,5,8'-tri(O-butyryl)-MB-530A-carboxylate	
	288. Ethyl 3,5,8'-tri(O-butyryl)-MB-530A-carboxylate	
	289. Butyl 3,5,8'-tri(O-butyryl)-MB-530A-carboxylate	
	290. Benzyl 3,5,8'-tri(O-butyryl)-MB-530A-carboxylate	
30	291. Pivaloyloxymethyl 3,5,8'-tri(O-butyryl)-M-530A-carboxylate	30
	292. Phenacyl 3,5,8'-tri(O-butyryl)-MB-530A-carboxylate	
	293. Sodium 3,5-di(O-acetyl)-ML-236B-carboxylate	
	294. Potassium 3,5-di(O-acetyl)-ML-236B-carboxylate	
35	295. Aluminum tris[3,5-di(O-acetyl)-ML-236B-carboxylate]	35
	296. Calcium bis[3,5-di(O-acetyl)-ML-236B-carboxylate]	
	297. Methyl 3,5-di(O-acetyl)-ML-236B-carboxylate	
	298. Ethyl 3,5-di(O-acetyl)-ML-236B-carboxylate	
	299. Isopropyl 3,5-di(O-acetyl)-ML-236B-carboxylate	
40	300. Butyl 3,5-di(O-acetyl)-ML-236B-carboxylate	40
	301. Benzyl 3,5-di(O-acetyl)-ML-236B-carboxylate	
	302. Pivaloyloxymethyl 3,5-di(O-acetyl)-ML-236B-carboxylate	
	303. Ethoxymethyl 3,5-di(O-acetyl)-ML-236B-carboxylate	
	304. Phenacyl 3,5-di(O-acetyl)-ML-236B-carboxylate	
45	305. Sodium 3,5-di(O-acetyl)-MB-530B-carboxylate	45
	306. Potassium 3,5-di(O-acetyl)-MB-530B-carboxylate	
	307. Calcium bis[3,5-di(O-acetyl)-MB-530B-carboxylate]	
	308. Aluminum tri[3,5-di(O-acetyl)-MB-530B-carboxylate]	
	309. Methyl 3,5-di(O-acetyl)-MB-530B-carboxylate	
	310. Ethyl 3,5-di(O-acetyl)-MB-530B-carboxylate	
50	311. Isopropyl 3,5-di(O-acetyl)-MB-530B-carboxylate	50
	312. Butyl 3,5-di(O-acetyl)-MB-530B-carboxylate	
	313. Benzyl 3,5-di(O-acetyl)-MB-530B-carboxylate	
	314. Pivaloyloxymethyl 3,5-di(O-acetyl)-MB-530B-carboxylate	
55	315. Methoxymethyl 3,5-di(O-acetyl)-MB-530B-carboxylate	55
	316. Ethoxymethyl 3,5-di(O-acetyl)-MB-530B-carboxylate	
	317. Phenacyl 3,5-di(O-acetyl)-MB-530B-carboxylate	
	318. Sodium 3,5-di(O-propionyl)-ML-236B-carboxylate	
	319. Methyl 3,5-di(O-propionyl)-ML-236B-carboxylate	
	320. Butyl 3,5-di(O-propionyl)-ML-236B-carboxylate	
60	321. Benzyl 3,5-di(O-propionyl)-ML-236B-carboxylate	60
	322. Sodium 3,5-di(O-propionyl)-MB-530B-carboxylate	
	323. Methyl 3,5-di(O-propionyl)-MB-530B-carboxylate	
	324. Butyl 3,5-di(O-propionyl)-MB-530B-carboxylate	
	325. Benzyl 3,5-di(O-propionyl)-MB-530B-carboxylate	
65	326. Sodium 3,5-di(O-butyryl)-ML-236B-carboxylate	65

	327. Methyl 3,5-di(O-butyryl)-ML-236B-carboxylate	
	328. Sodium 3,5-di(O-butyryl)-MB-530B-carboxylate	
	329. Methyl 3,5-di(O-butyryl)-MB-530B-carboxylate	
	330. Sodium 3,5-di(O-valeryl)-ML-236B-carboxylate	
5	331. Potassium 3,5-di(O-valeryl)-ML-236B-carboxylate	5
	332. Sodium 3,5-di(O-valeryl)-MB-530B-carboxylate	
	333. Potassium 3,5-di(O-valeryl)-MB-530B-carboxylate	
	334. Sodium 3,5-di(O-isovaleryl)-ML-236B-carboxylate	
	335. Sodium 3,5-di(O-isovaleryl)-MB-530B-carboxylate	
10	336. Sodium 3,5-di(O-stearoyl)-ML-236B-carboxylate	10
	337. Sodium 3,5-di(O-stearoyl)-MB-530B-carboxylate	
	338. Sodium 3,5-di(O-oleoyl)-ML-236B-carboxylate	
	339. Sodium 3,5-di(O-linoleoyl)-ML-236B-carboxylate	
	340. Sodium 3,5-di(O-linoleoyl)-MB-530B-carboxylate	
15	341. Sodium 3,5-di(O-benzoyl)-ML-236B-carboxylate	15
	342. Sodium 3,5-di(O-benzoyl)-MB-530B-carboxylate	
	343. Sodium 3,5-di(O-phenylacetyl)-ML-236B-carboxylate	
	344. Methyl 3,5-di(O-phenylacetyl)-ML-236B-carboxylate	
	345. Sodium 3,5-di(O-phenylacetyl)-MB-530B-carboxylate	
20	346. Methyl 3,5-di(O-phenylacetyl)-MB-530B-carboxylate	20
	347. Sodium 3,5-di(O-cyclopentanecarbonyl)-ML-236B-carboxylate	
	348. Sodium 3,5-di(O-cyclopentanecarbonyl)-MB-530B-carboxylate	
	349. Sodium 3,5-di(O-cyclohexanecarbonyl)-ML-236B-carboxylate	
	350. Sodium 3,5-di(O-cyclohexanecarbonyl)-MB-530B-carboxylate	
25	351. Sodium 3,5-di(O-thenoyl)-ML-236B-carboxylate	25
	352. Sodium 3,5-di(O-thenoyl)-MB-530B-carboxylate	
	353. Sodium 3,5-di(O-furoyl)-ML-236B-carboxylate	
	354. Sodium 3,5-di(O-furoyl)-MB-530B-carboxylate	
	355. Sodium 3,5-di(O-thienylacetyl)-ML-236B-carboxylate	
30	356. Sodium 3,5-di(O-thienylacetyl)-MB-530B-carboxylate	30
	357. Sodium 3,5-di(O-methanesulphonyl)-ML-236B-carboxylate	
	358. Sodium 3,5-di(O-methanesulphonyl)-MB-530B-carboxylate	
	359. Trisodium 3,5-di(O-phosphoryl)-ML-236B-carboxylate	
	360. Trisodium 3,5-di(O-phosphoryl)-MB-530B-carboxylate	
35	361. Sodium 3,5-di(O-acetyl)-8'-O-propionyl-ML-236A-carboxylate	35
	362. Methyl 3,5-di(O-acetyl)-8'-O-propionyl-ML-236A-carboxylate	
	363. Butyl 3,5-di(O-acetyl)-8'-O-propionyl-ML-236A-carboxylate	
	364. Benzyl 3,5-di(O-acetyl)-8'-O-propionyl-ML-236A-carboxylate	
	365. Sodium 3,5-di(O-acetyl)-8'-O-propionyl-MB-530A-carboxylate	
40	366. Methyl 3,5-di(O-acetyl)-8'-O-propionyl-MB-530A-carboxylate	40
	367. Sodium 3,5-di(O-acetyl)-8'-O-butyryl-ML-236A-carboxylate	
	368. Methyl 3,5-di(O-acetyl)-8'-O-butyryl-ML-236A-carboxylate	
	369. Butyl 3,5-di(O-acetyl)-8'-O-butyryl-MB-530A-carboxylate	
	370. Sodium 3,5-di(O-acetyl)-8'-O-butyryl-MB-530A-carboxylate	
45	371. Methyl 3,5-di(O-acetyl)-8'-O-butyryl-MB-530A-carboxylate	45
	372. Butyl 3,5-di(O-acetyl)-8'-O-butyryl-MB-530A-carboxylate	
	373. Sodium 3,5-di(O-butyryl)-8'-O-acetyl-ML-236A-carboxylate	
	374. Sodium 3,5-di(O-butyryl)-8'-O-acetyl-MB-530A-carboxylate	
	375. Sodium 3,5-di(O-acetyl)-8'-O-benzoyl-ML-236A-carboxylate	
50	376. Sodium 3,5-di(O-acetyl)-8'-O-benzoyl-MB-530A-carboxylate	50
	377. Sodium 3,5-di(O-benzoyl)-8'-O-acetyl-ML-236A-carboxylate	
	378. Methyl 3,5-di(O-benzoyl)-8'-O-acetyl-ML-236A-carboxylate	
	379. Sodium 3,5-di(O-benzoyl)-8'-O-acetyl-MB-530A-carboxylate	
	380. Methyl 3,5-di(O-benzoyl)-8'-O-acetyl-MB-530A-carboxylate	
55	Of these compounds, particularly preferred compounds are the following:	55
	Sodium ML-236A-carboxylate	
	Sodium MB-530A-carboxylate	
	Sodium 8'-O-butyryl-ML-236A-carboxylate	
	Sodium 8'-O-hexanoyl-ML-236A-carboxylate	
60	Ethyl 8'-O-butyryl-ML-236A-carboxylate	60
	Ethyl 8'-O-hexanoyl-ML-236A-carboxylate	
	Butyl 8'-O-butyryl-ML-236A-carboxylate	
	Butyl 8'-O-(4-pentenoyl)-ML-236A-carboxylate	
	Butyl 8'-O-isovaleryl-MB-530A-carboxylate	

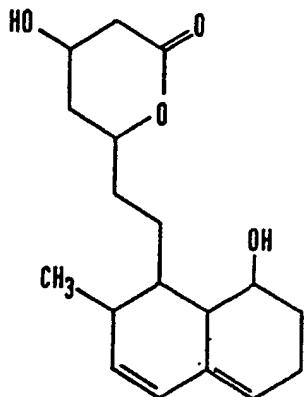
Benzyl 8'-O-butyryl-MB-236A-carboxylate
 Benzyl 8'-O-hexanoyl-ML-236A-carboxylate
 Phenacyl 8'-O-butyryl-MB-530A-carboxylate
 Butyl 3,5-di(O-acetyl)-ML-236B-carboxylate
 Butyl 3,5-di(O-benzoyl)-ML-236B-carboxylate.

5 5

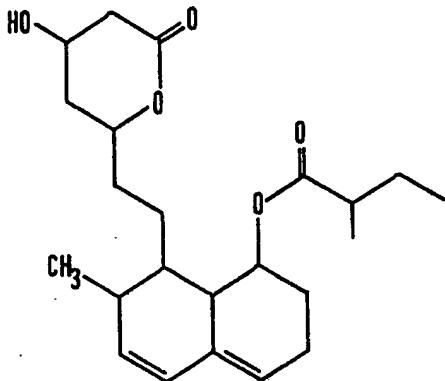
The compounds of the invention may be prepared by a variety of processes, all of which ultimately start from ML-236A, MB-236B, MB-530A, MB-530B, ML-236A carboxylic acid and MB-530A carboxylic acid, all of which may be prepared by cultivating appropriate microorganisms as described in the prior art hereinbefore referred to and as specifically illustrated hereafter in the

10 Preparations. The chemical structures of these compounds are as follows: 10

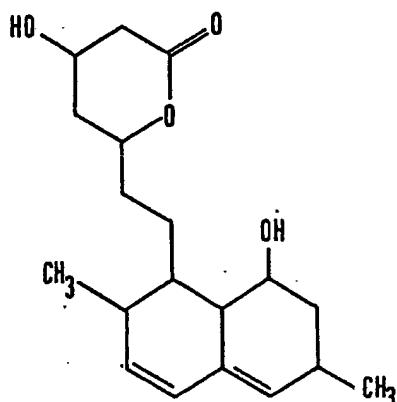
ML-236A



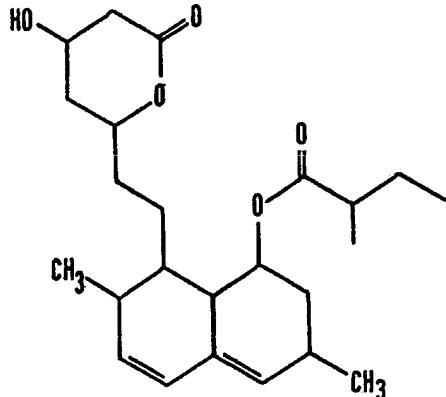
ML-236B



ML-530A

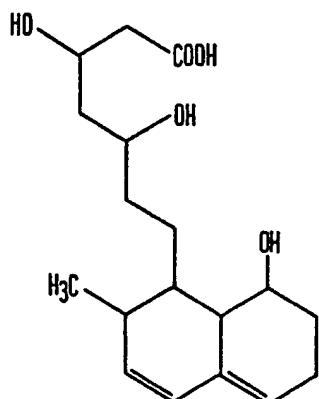


MB-530B



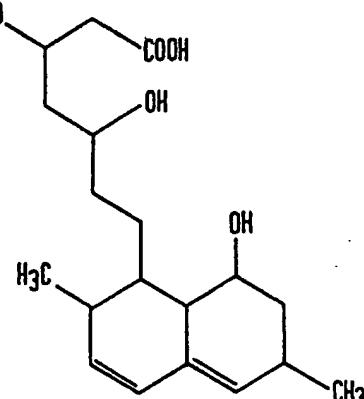
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ML-236A carboxylic acid



15

MB-530A carboxylic acid



Metal salts, and especially the alkali metal salts, of ML-236A and MB-530A may be prepared by cultivating an appropriate microorganism and then recovering the desired salt from the culture broth.

Specifically, salts of ML-236A carboxylic acid may be prepared by cultivating an ML-236A-producing microorganism of the genus *Penicillium* and recovering the ML-236A carboxylic acid salt from the culture broth, whilst MB-530A carboxylic acid salts may be prepared by cultivating an MB-530A-producing microorganism of the genus *Monascus* and recovering the MB-530A carboxylic acid salt from the culture broth. 5

The microorganisms of the genus *Penicillium* are preferably *Penicillium citrinum*, *Penicillium chrysogenum* or *Penicillium notatum*, most preferably *Penicillium citrinum* SANK 18767 (FERM 2609), 10 *Penicillium citrinum* SANK 24467, *Penicillium citrinum* SANK 24567, *Penicillium chrysogenum* SANK 12768 (ATCC 10002) or *Penicillium notatum* SANK 24867.

The microorganisms of the genus *Monascus* are preferably strains of *Monascus ruber*, *Monascus anka*, *Monascus paxii*, *Monascus purpureus* or *Monascus vitreus*, preferably *Monascus ruber* SANK 11272 (IFO 9203), *Monascus ruber* SANK 17075 (CBS 832.70), *Monascus ruber* SANK 17175 (CBS 15 503.70), *Monascus ruber* SANK 17275 (ATCC 18199), *Monascus ruber* SANK 15177 (FERM 4956), *Monascus ruber* SANK 13778 (FERM 4959), *Monascus ruber* SANK 10671 (FERM 4958), *Monascus ruber* SANK 18174 (FERM 4957), *Monascus anka* SANK 10171 (IFO 6540), *Monascus paxii* SANK 11172 (IFO 8201), *Monascus purpureus* SANK 10271 (IFO 4513) or *Monascus vitreus* SANK 10960 (NIHS 609, e-609, FERM 4960).

20 All of these microorganisms are available from recognized culture collections, as indicated by the following codes:

IFO	=Institute for Fermentation, Osaka, Japan;
FERM	=Fermentation Research Institute, Agency of Industrial Science and Technology, Ministry of International Trade and Industry, Japan;
25 NIHS	=National Institute of Hygienic Sciences, Japan;
CBS	=Centraal Bureau Voor Schimmelcultures, Netherlands,
ATCC	=American Type Culture Collection, Maryland, U.S.A.

Apart from the strains of microorganisms mentioned above, any microorganism of the genus *Penicillium* or *Monascus*, including varieties and mutants, which are capable of producing ML-236A or 30 MB-530A, respectively, may be employed in the process of the present invention.

The ML-236A and MB-530A salts may be produced by cultivating the chosen microorganism in a culture broth under aerobic conditions, using the techniques well-known in the art for cultivation of fungi and other microorganisms. For example, the chosen strain of *Penicillium* or *Monascus* may first be cultivated on a suitable medium and then the produced microorganism may be collected and 35 inoculated into and cultivated on another culture medium to produce the desired ML-236A or MB-530A; the culture medium used for the multiplication of the microorganism and the culture medium used for the production of the ML-236A or MB-530A may be the same or different. Any culture medium well-known in the art for the cultivation of fungi may be employed, provided that it contains, as is well-known, the necessary nutrient materials, especially an assimilable carbon source and an 40 assimilable nitrogen source. Examples of suitable sources of assimilable carbon are glucose, maltose, dextrin, starch, lactose, sucrose and glycerine. Of these sources, glucose and glycerine are particularly preferred for the production of ML-236A and MB-530A. Examples of suitable sources of assimilable nitrogen are peptone, meat extract, yeast, yeast extract, soybean meal, peanut meal, corn steep liquor, rice bran and inorganic nitrogen sources. When producing the ML-236A or MB-530A, an inorganic salt 45 and/or a metal salt may, if necessary, be added to the culture medium. Furthermore, if necessary, a minor amount of a heavy metal may also be added. In certain cases, it is believed possible that the fungus of the genus *Penicillium* or *Monascus* may produce the desired ML-236A or MB-530A carboxylic acid salt directly, whilst in other cases the fungus will produce the ML-236A or MB-530A first and this is then converted to the desired salt in the course of a routine separation and purification 50 procedure. Where the salts are to be produced directly by the fungus, it is important that there should be present in the culture medium or within the body of the fungus metal ions corresponding to the metal salt which it is desired to produce.

The microorganism is preferably cultivated under aerobic conditions using cultivation methods well-known in the art, for example solid culture, shaken culture or culture under aeration and agitation. 55 The microorganisms will grow over a wide temperature range, e.g. from 7 to 35°C, but, especially when the microorganism is grown for the purpose of producing ML-236A or MB-530A or a carboxylic acid salt thereof, the more preferred cultivation temperature is within the range from 20 to 30°C.

During the cultivation of the microorganism, the production of the desired ML-236A or MB-530A or carboxylic acid salt thereof may be monitored by sampling the culture medium and measuring the 60 physiological activity of the medium by appropriate tests. Cultivation may then be continued until a substantial accumulation of active material has been achieved in the culture medium, at which time the ML-236A or MB-530A carboxylic acid salt may be isolated and recovered from the culture medium and the tissues of the microorganism by any suitable combination of isolation techniques,

chosen having regard to their physical and chemical properties. For example, any or all of the following isolation techniques may be employed: extraction of the liquor from the culture broth with a hydrophilic solvent (such as diethyl ether, ethyl acetate or chloroform); extraction of the organism with a hydrophilic solvent (such as acetone or an alcohol); concentration, e.g. by evaporating off all or part of the solvent under reduced pressure; dissolution into a more polar solvent (such as an acetone or an alcohol); removal of impurities with a less polar solvent (such as petroleum ether or hexane); gel filtration through a column of a material such as "Sephadex" (a registered Trade Mark for a material available from Pharmacia Co. Limited, U.S.A.); absorptive chromatography with active carbon or silica gel; rapid liquid chromatography; conversion to ML-236A or MB-530A itself or its parent acid; direct purification in the form of the metal salt; and other similar methods. By using a suitable combination of these techniques, the desired salt can be isolated from the culture broth as a pure substance.

As described in the prior art, ML-236A, ML-236B, MB-530A, MB-530B, ML-236A carboxylic acid and MB-530A carboxylic acid, all of which are important starting materials for the preparation of certain of the compounds of the present invention, may also be produced using the microorganisms and techniques described above.

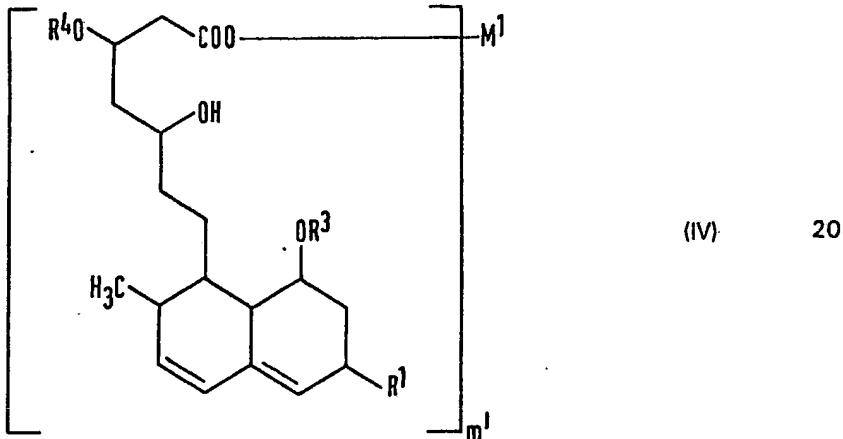
Others of the compounds of the invention may be prepared by the following methods.

Method 1

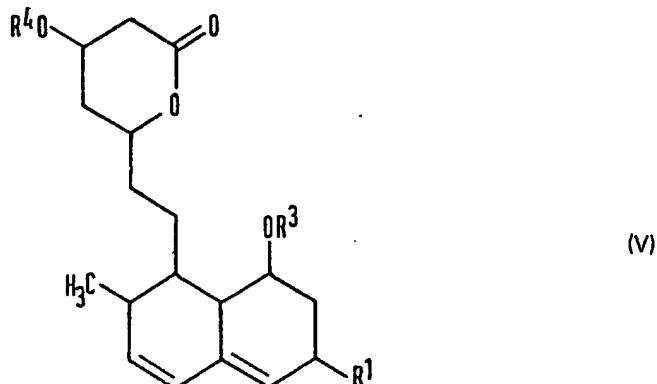
Preparation of Salts

Carboxylic acid salts of formula (IV):

20



(in which R¹, R³ and R⁴ are as defined above; M¹ represents the cationic moiety of a salt; and m' represents the valency of M¹) may be prepared by hydrolyzing a lactone of formula (V):



(in which R¹, R³ and R⁴ are as defined above) and, if necessary converting the carboxyl group of the product thus obtained to the corresponding salt.

The hydrolysis may be carried out by any of the methods well-known in the art for conversion of lactones to the corresponding hydroxyacid. If desired, the hydroxyacid may then be extracted with a suitable organic solvent and then saltified by reaction with a base corresponding to the salt which it is desired to produce, for example with a metal hydroxide or carbonate, ammonia, organic amine or

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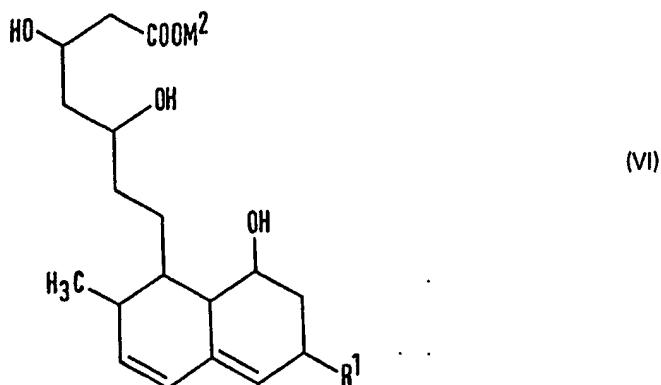
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amino acid. However, where it is desired to prepare a metal salt (i.e. M¹ represents a metal atom), it is often most convenient to effect the hydrolysis and salification in a single step by using a basic compound of the metal, preferably the metal hydroxide, in an amount at least equimolar with respect to the lactone of formula (V), to effect hydrolysis. In this case, the metal salt of formula (IV) is produced

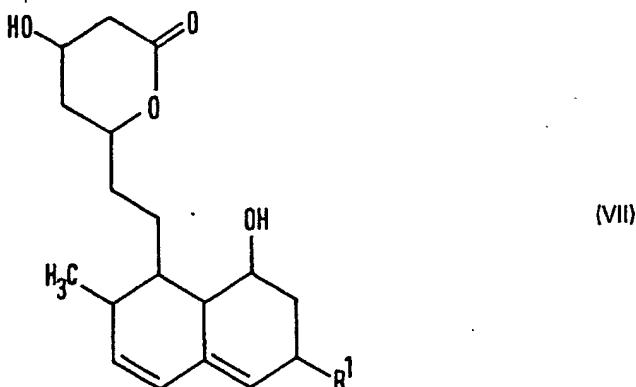
5 directly and may be obtained simply by distilling off the solvent from the reaction mixture.

The hydrolysis may be effected by conventional methods, for example by contacting the lactone (V) with a dilute (e.g. from 0.1 to 0.2N) aqueous solution of the metal hydroxide, preferably an alkali metal hydroxide such as sodium hydroxide or potassium hydroxide, in water or an aqueous organic solution, e.g. an aqueous alcohol or aqueous dioxan. The hydrolysis may be effected over a wide range 10 of temperatures, for example at room temperature or at an elevated temperature, e.g. from 50 to 100°C. The time required for the reaction will vary over a wide range, depending upon the reagents and the reaction temperature, but the reaction will normally require several hours.

In a preferred embodiment of this Method an alkali metal salt of formula (VI):

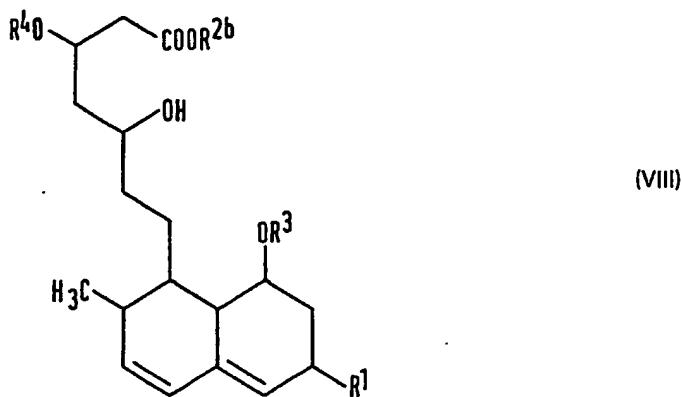


15 (in which R¹ is as defined above and M² represents an alkali metal atom) may be prepared by 15 hydrolyzing, in an alkaline solution containing said alkali metal atom, a lactone of formula (VII):



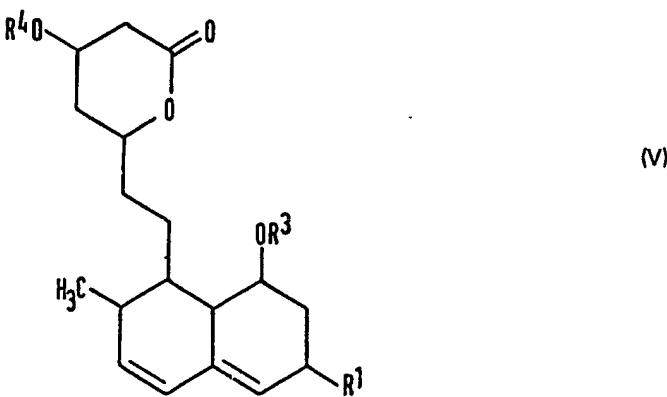
(in which R¹ is as defined above). In this case, M² preferably represents a sodium atom and the alkaline solution is preferably an aqueous solution of sodium hydroxide.

Method 2
Preparation of Ester from The Corresponding Lactone
 Carboxylic acid esters of formula (VIII):



5 (wherein:
 R¹ represents a hydrogen atom or a methyl group;
 R³ and R⁴ are the same or different and each represents a hydrogen atom or an acyl group,
 provided that, when R³ represents a 2-methylbutyryl group, R⁴ represents an acyl group; and
 R^{2b} represents an alkyl group or an aralkyl group) may be prepared by reacting a lactone of
 10 formula (V):

10



(in which R¹, R³ and R⁴ are as defined above) with an alcohol in the presence of an acid catalyst.
 Suitable acid catalysts include: inorganic acids such as hydrochloric acid or sulphuric acid; Lewis acids, such as boron trifluoride; and acidic ion-exchange resins. The reaction may be carried out in the
 15 presence of a suitable inert organic solvent, for example benzene, diethyl ether or chloroform. However, where the alcohol, which is one of the reagents, is a liquid, we prefer to use this as the solvent.
 Although the reaction will take place over a wide temperature range, it is preferably conducted with heating, for example at a temperature of from 50°C to the boiling point of the solvent. After completion
 20 of the reaction, the desired product may be recovered from the reaction mixture by conventional methods. For example, when the catalyst employed is an ion-exchange resin, this resin is filtered off and then the solvent is distilled off to give the desired compound. If the catalyst is an inorganic acid or a Lewis acid, this is neutralized and then the solvent is distilled off, the residue is extracted with a suitable solvent, which is then distilled from the extract to give the desired product.

The same process may be employed for the preparation of other esters than alkyl and aralkyl
 25 esters, by using appropriate hydroxy- compounds or functional equivalents thereof; for example, compounds of formula (I) where R² represents a bivalent aliphatic hydrocarbon group may be prepared by replacing the alcohol used in the above process by a glycol. Also, in place of the acid-catalyzed
 solvolysis process described above, it is possible to use any other conventional solvolysis technique to
 30 produce any compound of formula (I) in which R² represents an ester residue capable of formation by solvolysis of a lactone.

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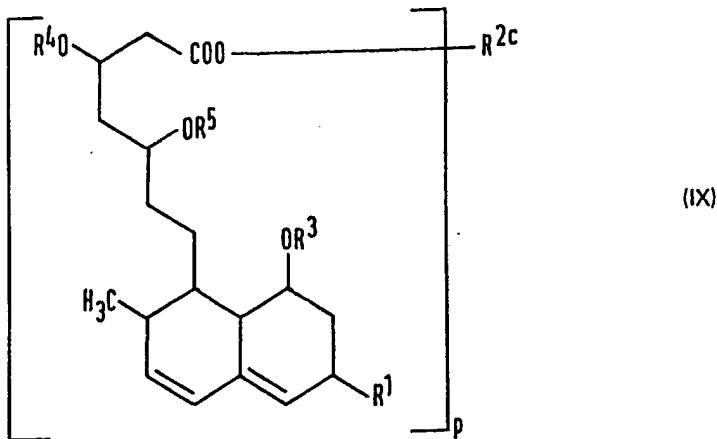
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Method 3
Preparation of Esters from The Corresponding Metal Salt
 Carboxylic acid esters of formula (IX):

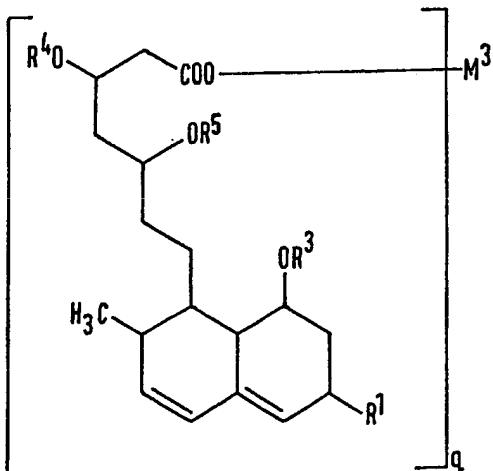


5 (wherein:
 R^1, R^3, R^4 and R^5 are as defined above;
 R^{2c} represents the alcoholic moiety of an ester; and
 p represents the valence of R^{2c})
 can be prepared by reacting a metal salt of formula (X):

5

10

(X) 10



(wherein R^1, R^3, R^4 and R^5 are as defined above;
 M^3 represents a metal atom, preferably an alkali metal or alkaline earth metal atom; and
 q represents the valence of M^3) with an esterifying agent, preferably an esterifying agent of
 formula $R^{2c}-X$

15 15 (in which X represents a halogen atom, for example a chlorine or bromine atom).

This reaction may be carried out using procedures conventional for alkylating carboxylic acid metal salts. For example, the metal salt of formula (X) may be contacted with the esterifying agent in the presence of an inert organic solvent, to give the desired ester of formula (IX). There is no particular limitation upon the nature of the solvent employed, provided that it has no adverse effect upon the

20 reaction and preferred solvents include dimethylformamide, dimethyl sulphoxide, tetrahydrofuran, hexamethylphosphoryltriamide, acetone and methyl ethyl ketone. The reaction may be carried out over a wide range of temperatures, for example at room temperature or at an elevated temperature, but we normally prefer to carry out the reaction at about room temperature. The time required for the reaction will, of course, depend upon the reaction temperature and upon the reagents employed, but will

25 normally range from 1 to 20 hours. The desired product may be recovered from the reaction mixture by conventional means, for example by diluting the reaction mixture with water, extracting the mixture with a water-immiscible solvent and distilling off the solvent from the extract.

15

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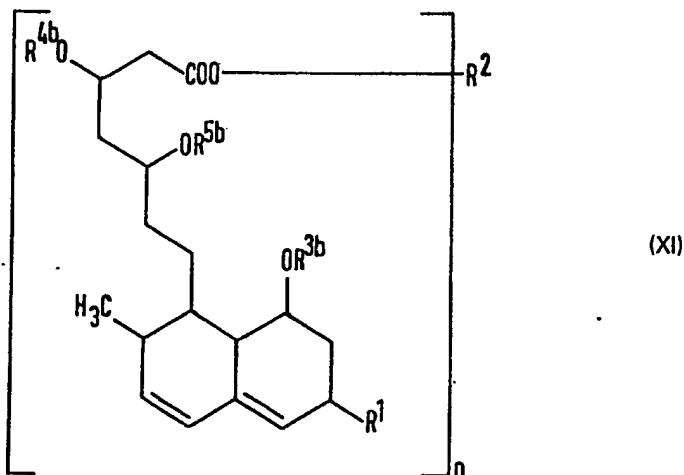
The esterifying agent employed is preferably an alkyl halide, an aralkyl halide or a phenacyl halide and the metal salt of formula (X) is preferably an alkali metal salt (i.e. M³ represents an alkali metal atom). This alkali metal salt is preferably formed *in situ* by another reaction, for example that described in Method 1, prior to the reaction with the esterifying agent.

5 It is particularly preferred that the compounds employed should be those compounds in which: 5
 R¹ represents a hydrogen atom or a methyl group;
 R³ represents a hydrogen atom, a C₂—C₆ alkanoyl group or a C₃—C₆ alkenoyl group;
 R⁴ and R⁵ are the same or different and each represents a hydrogen atom, a C₂—C₆ alkanoyl group or a benzoyl group, provided that, when R³ represents a 2-methylbutyryl group, R⁴ and R⁵ both represent acyl groups; and
 10 M³ represents an alkali metal atom; and that the esterifying agent should be a benzyl halide or a phenacyl halide.

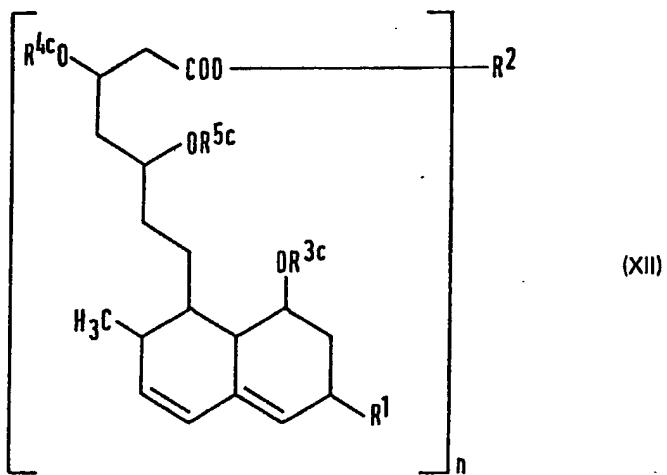
Method 4

Preparation of 3-acyl, 5-acyl and 8'-acyl Derivatives

15 A triacyl compound of formula (XI): 15

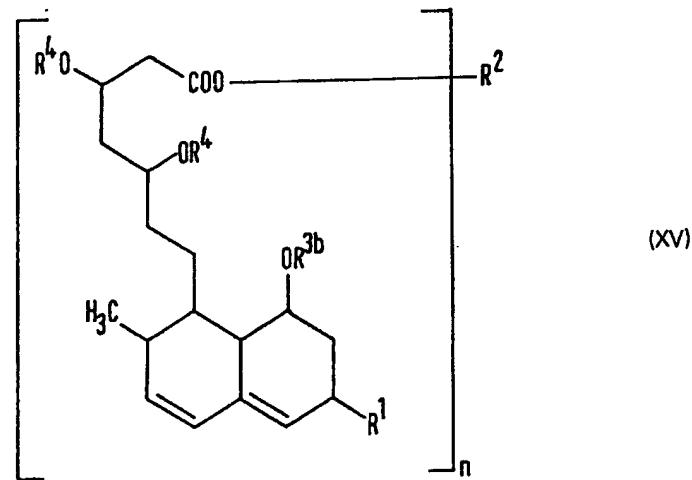
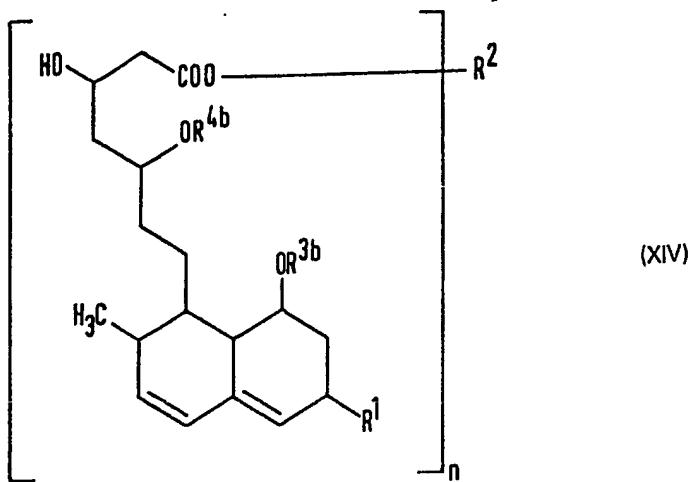
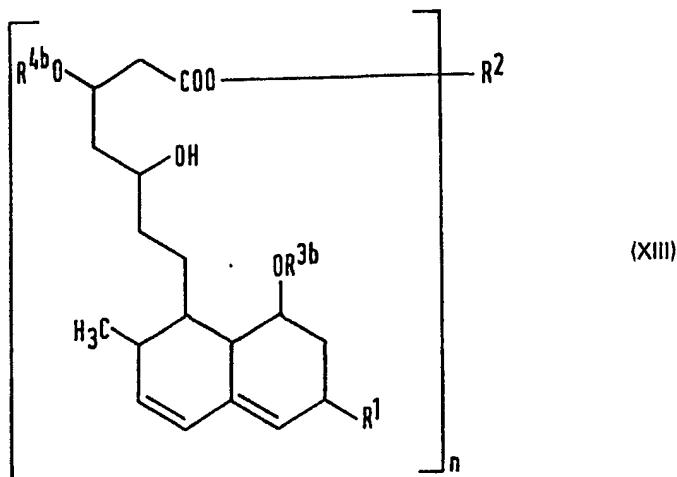


(in which R¹, R² and n are as defined above and R^{3b}, R^{4b} and R^{5b} are the same or different and each represents an acyl group) may be prepared by acylating a compound of formula (XII):



20 (in which R¹, R² and n are as defined above and R^{3c}, R^{4c} and R^{5c} are the same or different and each represents a hydrogen atom or an acyl group, provided that at least one of R^{3c}, R^{4c} and R^{5c} represents a hydrogen atom). 20

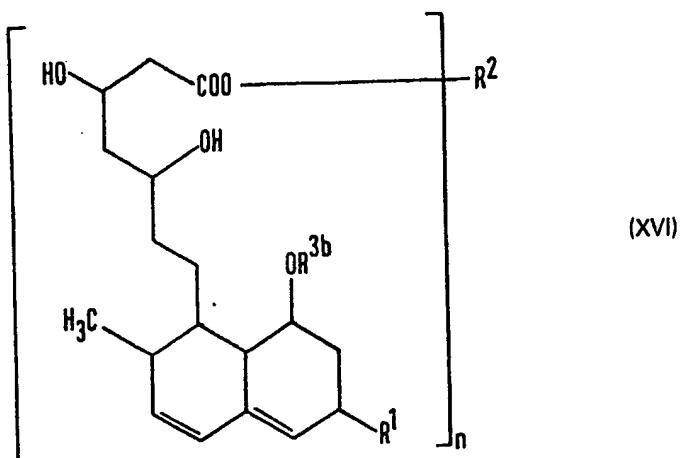
Compounds of formulae (XIII), (XIV) and (XV):



5 (wherein:

- R¹, R² and n are as defined above;
- R⁴ represents a hydrogen atom or an acyl group;
- R^{3b} represents an acyl group; and

R^{4b} represents an acyl group) may be prepared by acylating a compound of formula (XVI):



(wherein R^1 , R^2 , n and R^{3b} are as defined above). By appropriate choice of conditions, it is possible to 5
prepare either a single one of the compounds of formulae (XIII), (XIV) and (XV), a mixture of any two or
a mixture of all three. The desired compound or compounds may then be isolated from the reaction
mixture.

5

The acylation reaction itself is preferably carried out by either of the following processes:

(A) Acylation Using a Reactive Derivative of An Acid

In this process, the compound of formula (XII) or (XVI) is contacted with a reactive derivative of 10
the acid having the desired acyl group, for example an acid halide (such as an acid chloride or acid
bromide), an acid anhydride or a mixed acid anhydride (for example a mixed acid anhydride of an acid
with a chlorocarbonic ester or a sulphonic acid chloride). The reaction is preferably carried out in the
presence of a solvent and also preferably in the presence of a base. There is no particular limitation
upon the nature of the solvent to be employed, provided that it has no adverse effect upon the reaction
15 and suitable solvents include chloroform, methylene chloride, diethyl ether, tetrahydrofuran and dioxan. Preferred bases include such organic amines as pyridine, 4-(*N,N*-dimethylamino)pyridine, quinoline,
triethylamine, *N*-methylmorpholine, *N*-methylpiperidine and *N,N*-dimethylaniline. Where the amine
employed is a liquid at the reaction temperature, for example pyridine, it may also serve as the solvent.
The reaction is preferably carried out at room temperature or with cooling in order to control side
20 reactions, but it will proceed at elevated temperatures. The reaction time will depend upon the reaction
temperature and upon the nature of the reagents but it will normally be complete within a period of
from 10 minutes to 10 hours. After completion of the reaction, the desired product may be recovered
by conventional means, for example by diluting the reaction mixture with water, extracting the mixture
with a water-immiscible solvent and distilling the solvent from the extract.

10

(B) Acylation With a Condensing Agent

25

This reaction may be carried out under conventional conditions employing a free acid
corresponding to the acyl group which it is desired to introduce in the presence of a condensing agent
and, in this case, the compound of formula (XII) or (XVI) is simply contacted with the acid in the
presence of the condensing agent. The condensing agent is preferably a dehydrating agent, for
30 example a carbodiimide, such as dicyclohexylcarbodiimide. The reaction is normally carried out in the
presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the
reaction. Suitable solvents include dimethylformamide, dimethylacetamide, acetonitrile, pyridine,
methylene chloride, chloroform and dioxan. The reaction may be carried out over a wide temperature
range, but, in order to control side reactions, we normally prefer to conduct it at room temperature or
35 with cooling; however, the reaction will also proceed at elevated temperatures. The time required for
the reaction will vary depending upon the reaction temperature and the reagents employed, but the
reaction will normally be complete within a period of from 1 to 20 hours. The desired compound may
then be recovered from the reaction mixture by conventional means, for example by filtering off
insolubles, diluting the filtrate with water, extracting the resulting mixture with a water-immiscible
40 solvent and then distilling the solvent from the extract to give the desired product.

30

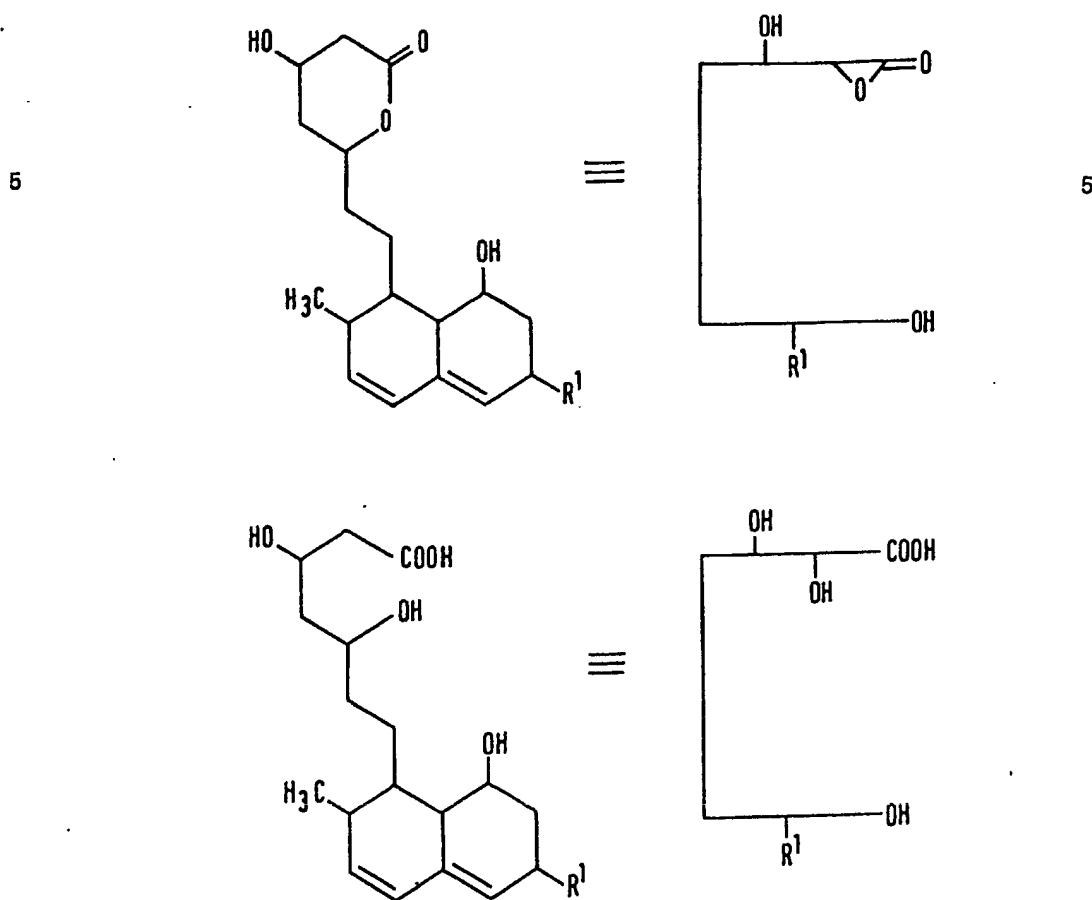
In the case of both of the above acylation reactions, where the starting material contains two or
more free hydroxy groups, any of the mono, di or tri- acyl derivatives can be obtained by controlling the
amount of acylating agent employed. If a mixture of these compounds is obtained, the separate
compounds may be isolated using conventional isolation techniques, for example chromatography on
45 silica gel.

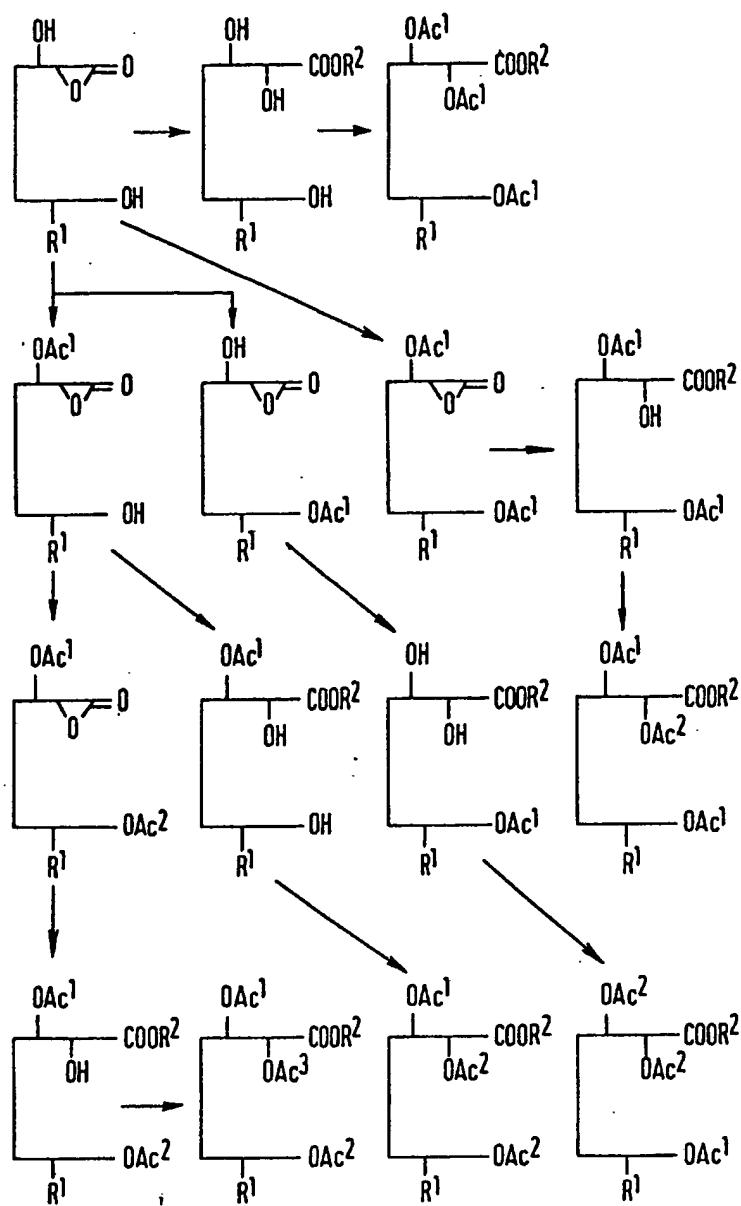
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The compounds of the invention may ultimately be prepared from the fermentation products ML-236A, ML-236B, Mb-530A and MB-530B or their corresponding carboxylic acids or carboxylic acid salts by any combination of the above reactions. These reactions are summarized in the following reaction scheme, in which the chemical structures of the compounds are simplified as follows:





In the above reaction scheme, Ac¹, Ac² and Ac³ are the same or different and each represents an acyl group.

The compounds of the invention have been found to inhibit the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), which is the rate-determining enzyme in the biosynthesis of cholesterol. According to the method of Knauss, et al. [J. Biol. Chem., 234, 2835 (1959)], the inhibitory activities of the compounds of the invention against the biosynthesis of cholesterol, expressed as their ID₅₀ values (i.e. the concentration required to inhibit the biosynthesis of cholesterol by 50%), varied from 1.0 to 0.03 µg/ml. Moreover, sodium salts, i.e. compounds of formula (I) in which R² represents a sodium atom, were found to be adsorbed during an *in vivo* test far better than the corresponding lactone and in general it is believed that the compounds of the invention have improved bioavailability compared with the corresponding lactones.

The compounds of the invention may be administered for the treatment of hypercholesterolaemia by any conventional means, but they are preferably administered in the form of tablets or capsules. The daily dose will vary depending upon the age, body weight and condition of the patient, but in general the compounds of the invention are preferably administered in an amount of from 1 mg to 10 mg per day, in a single dose or in divided doses.

The preparation of the compounds of the invention is further illustrated by the following Examples. Preparation of certain of the starting materials used in these Examples is illustrated by

Preparations 1—4 and other starting materials may be prepared in a manner similar to that described in these Preparations. The preparation of ML-236A and ML-236B are described in more detail in US Patent Specification No. 3,983,140 and the preparation of MB-530 (Monacolin K) is described in United Kingdom Patent Applications No. 2046737 and No. 2049664.

5

5 Preparation 1

3-O-Butyryl-ML-236A

918 mg of ML-236A were dissolved in 5 ml of pyridine, and 1 ml of butyric anhydride was added dropwise thereto at room temperature. After leaving the reaction mixture to stand overnight, it was diluted with water and extracted with diethyl ether. The extract was washed successively with water, a saturated aqueous solution of sodium bicarbonate, water, 1N hydrochloric acid and water and dried over anhydrous sodium sulphate. The solvent was distilled off from the solution and the residue was subjected to column chromatography through silica gel, eluted with a 5:1 by volume mixture of benzene and ethyl acetate, to give 930 mg of the desired product as a colourless oily substance.

10

Elemental analysis:

Calculated for $C_{22}H_{32}O_5$: C, 70.21%; H, 8.51%.
Found: C, 69.95%; H, 8.69%.

15

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.95 (3H, triplet);
4.27 (1H, multiplet);
5.32 (1H, multiplet).

20

Infrared Absorption Spectrum (liquid film) ν_{max} cm^{-1} :

3460, 1740.

Preparation 2

3,8-Di(O-butyryl)-ML-236A

306 mg of ML-236A and 0.5 ml of pyridine were dissolved in 3 ml of methylene chloride, and 0.5 ml of butyryl chloride was added dropwise thereto, with ice-cooling. The mixture was stirred at room temperature for 1 hour and then washed adding water. The organic layer was separated and dried over anhydrous sodium sulphate, after which the solvent was distilled off. The resulting residue was subjected to column chromatography through silica gel, eluted with a 10:1 by volume mixture of benzene and ethyl acetate, to afford 384 mg of the desired product as a colourless oily substance.

25

Elemental analysis:

Calculated for $C_{26}H_{38}O_6$: C, 69.96%; H, 8.52%.
Found: C, 70.14%; H, 8.31%.

30

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.93 (6H, triplet);
5.2—5.5 (2H, multiplet).

35

Infrared Absorption Spectrum (liquid film) ν_{max} cm^{-1} :

1735, 1250, 1175.

Preparation 3

40 8'-O-Butyryl-ML-236A

918 mg of ML-236A and 0.36 ml of pyridine were dissolved in 10 ml of methylene chloride. The solution was cooled in an ice bath, and 0.35 ml of butyryl chloride was added dropwise thereto. After being stirred for 1 hour, the mixture was diluted with water. The organic layer was separated, washed with water and dried over anhydrous sodium sulphate. The solvent was distilled off and the residue was subjected to column chromatography through silica gel. The 3,8'-diacyl compound (described in Preparation 2) was obtained by eluting with a 10:1 by volume mixture of benzene and ethyl acetate, the 3-acyl compound (described in Preparation 1) was obtained by eluting with a 5:1 by volume mixture of benzene and ethyl acetate, and 395 mg of the desired product were obtained as colourless crystals melting at 124—5°C from the eluate using a 2:1 by volume mixture of benzene and ethyl acetate.

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Elemental analysis:

Calculated for $C_{22}H_{32}O_5$: C, 70.21%; H, 8.51%.
Found: C, 70.25%; H, 8.50%.

45

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

55

0.95 (3H, triplet);
4.42 (1H, multiplet).

50

Infrared Absorption Spectrum (Nujol-trade mark) ν_{max} cm^{-1} :

3400, 1730, 1710.

Other acyl derivatives can be prepared by following the procedures described in these
60 Preparations.

60

Preparation 4**Preparation of MB-530A**

300 litres of a culture medium having a pH of 5.5 before sterilization and containing 5% w/v glucose, 0.5% w/v corn steep liquor, 2% w/v peptone (Kyokuto brand, available from Kyokuto Seiyaku KK, Japan) and 0.5% ammonium chloride were charged into a 600 litre fermenter and inoculated with a culture of *Monascus ruber* SANK 15177 (FERM 4956, NRRL 12081). Cultivation of the microorganism was continued for 120 hours at 27°C with an aeration rate of 300 litres/minute and agitation at 190 revolutions per minute.

At the end of this time, the culture broth was filtered in a filter press to give a filtrate and a filter cake comprising wet cells of the microorganism.

The filtrate was adjusted to a pH of 3.0 by the addition of 6N hydrochloric acid and then extracted with 400 litres of ethyl acetate. The extract (about 400 litres) was concentrated by evaporation under reduced pressure and then dehydrated over anhydrous sodium sulphate, after which it was evaporated to dryness, to give about 60 g of an oily product. This oily product was washed with ethylcyclohexane and with hexane and the residue (20 g) was separated by chromatography using a liquid chromatography device for large volume sampling (System 500 liquid chromatography, produced by Waters Co., U.S.A.), eluted with 60% v/v aqueous methanol. Fractions having a chromatographic retention time of 6 minutes were collected and concentrated by evaporation under reduced pressure to give 100 mg of the desired MB-530A as an oily product. This oily MB-530A was recrystallized from a mixture of acetone and diethyl ether to give 57 mg of the desired product in the form of colourless needles having the following properties:

1. Melting Point: 92—93°C.
2. Elemental Analysis:
Calculated for $C_{19}H_{28}O_4$: C, 69.76%; H, 8.68%.
Found: C, 71.22%; H, 8.81%.
3. Molecular weight: 320 (by mass analysis).
4. Molecular formula: $C_{19}H_{28}O_4$.
5. Ultraviolet Absorption Spectrum: As shown in Figure 1 of the accompanying drawings.
6. Infrared Absorption Spectrum: As shown in Figure 2 of the accompanying drawings.
7. Nuclear Magnetic Resonance Spectrum: As shown in Figure 3 of the accompanying drawings.
8. Solubility:
readily soluble in methanol, ethanol, acetone and ethyl acetate;
soluble in benzene;
insoluble in hexane and petroleum ether.
9. Colouration reaction:
a pink colour is seen when a thin layer chromatogram on silica gel of the compound is developed with 50% v/v sulphuric acid.
10. Inhibitory activity against the biosynthesis of cholesterol: a 50% inhibition of the synthesis of cholesterol in a rat liver is observed at a concentration of 0.04 µg/ml.

40 Example 1
Sodium ML-236A-carboxylate
0.4 g of ML-236A was added to 12 ml of 0.1N aqueous solution of sodium hydroxide, and the mixture was heated at 80—90°C for 2 hours. After completion of the reaction, insolubles were filtered off and the filtrate was lyophilized to afford 0.41 g of the desired product as a colourless powder.

45 Elemental analysis:
Calculated for $C_{18}H_{27}O_6Na$: C, 62.43%; H, 7.80%.
Found: C, 62.58%; H, 7.72%.

Example 2**Sodium 8'-O-butyryl-ML-236A-carboxylate**

50 0.75 g of 8'-O-butyryl-ML-236A was added to 20 ml of a 0.1N aqueous solution of sodium hydroxide, and the resulting mixture was heated at 80—90°C for 2 hours. After completion of the reaction, insolubles were filtered off and the filtrate was lyophilized to give 0.83 g of the desired product as a colourless powder.

Elemental analysis:
Calculated for $C_{22}H_{33}O_6Na$: C, 63.46%; H, 7.93%; Na, 5.53%.
Found: C, 63.54%, H, 7.90%; Na, 5.50%.

Nuclear Magnetic Resonance Spectrum (D_2O) δ ppm:
0.95 (3H, triplet);
4.15 (2H, triplet);
3.5—4.5 (2H, multiplet).

60 Infrared Absorption Spectrum (Nujol) ν_{max} cm⁻¹:
3450, 1730, 1580.

Example 3**Sodium 8'-O-hexanoyl-ML-236A-carboxylate**

0.88 g of 8'-O-hexanoyl-ML-236A was added to 20 ml of a 0.1N aqueous solution of sodium hydroxide. The mixture was treated in the same manner as described in Example 1, to give 0.84 g of the desired product as a colourless powder.

5

Elemental analysis:

Calculated for $C_{24}H_{37}O_6Na$: C, 64.86%; H, 8.33%; Na, 5.18%.
Found: C, 64.75%; H, 8.37%; Na, 5.25%.

Nuclear Magnetic Resonance Spectrum (D_2O) δ ppm:

10 0.87 (3H, triplet);
4.13 (2H, multiplet);
3.5—4.5 (2H, multiplet).

Infrared Absorption Spectrum (Nujol) ν_{max} cm⁻¹:
3450, 1730, 1580.

10

15

Example 4**Ethyl 8'-O-butyryl-ML-236A-carboxylate**

0.79 g of 8'-O-butyryl-ML-236A were dissolved in 10 ml of ethanol, and 1 g of a sulphonic acid-type strongly acidic cation exchange resin (sold under the trade name Dowex 50W) was added thereto. The mixture was heated at 60—70°C for 3 hours. After completion of the reaction, the

20

20 mixture was filtered and the filtrate was concentrated by evaporation under reduced pressure. The residue was purified by column chromatography through silica gel to afford 0.41 g of the desired product as a colourless oily substance.

Elemental analysis:

Calculated for $C_{24}H_{38}O_6$: C, 68.25%; H, 9.00%.
Found: C, 68.19%; H, 9.06%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

25 0.95 (3H, triplet);
1.23 (3H, triplet);
4.12 (2H, quartet);
3.5—4.5 (2H, multiplet).

Infrared Absorption Spectrum (liquid film) ν_{max} cm⁻¹:
3450, 1740.

25

30

Example 5**Ethyl 8'-O-hexanoyl-ML-236A-carboxylate**

35 0.9 g of 8'-O-hexanoyl-ML-236A was dissolved in 10 ml of ethanol, and 1.5 g of a sulphonic acid-type strongly acidic cation exchange resin were added thereto. The mixture was treated in the same manner as described in Example 3, to give 0.55 g of the desired product as a colourless oily substance.

35

Elemental analysis:

40 Calculated for $C_{26}H_{46}O_6$: C, 69.33%; H, 9.33%.
Found: C, 69.21%; H, 9.39%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

45 0.87 (3H, triplet);
1.25 (3H, triplet);
4.13 (2H, quartet);
3.5—4.5 (2H, multiplet).

Infrared Absorption Spectrum (liquid film) ν_{max} cm⁻¹:
3400, 1730, 1720.

40

45

Example 6**Butyl 8'-O-butyryl-ML-236A-carboxylate**

50 0.79 g of 8'-O-butyryl-ML-236A was dissolved in 10 ml of butanol, and 1.0 g of a sulphonic acid-type strongly acidic cation exchange resin was added thereto. The mixture was treated in the same manner as described in Example 3, to afford 0.59 g of the desired product as a colourless oily substance.

50

55

Elemental analysis:

55 Calculated for $C_{26}H_{42}O_6$: C, 69.33%; H, 9.33%.
Found: C, 69.25%; H, 9.40%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

60 0.95 (3H, triplet);
1.24 (3H, triplet);
4.12 (2H, triplet);
3.5—4.5 (2H, multiplet).

Infrared Absorption Spectrum (liquid film) ν_{max} cm⁻¹:
3440, 1730.

60

Example 7**Butyl 8'-O-(4-pentenoyl)-ML-236A-carboxylate**

Following the procedure described in Example 3, but using 0.92 g of 8'-O-(4-pentenoyl)-ML-236A, 10 ml of butanol and 1.0 g of the ion exchange resin, there was obtained 0.45 g of the desired product as a colourless oily substance.

Elemental analysis:

Calculated for $C_{27}H_{42}O_6$: C, 70.13%; H, 9.09%.

Found: C, 70.04%; H, 9.13%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

10 1.24 (3H, multiplet);

3.5—4.5 (4H, multiplet);

4.8—6.2 (8H, multiplet);

Infrared Absorption Spectrum (liquid film) ν_{max} cm⁻¹:

3400, 1730.

5

10

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Example 8**Butyl 8'-O-isovaleryl-MB-530A-carboxylate**

Following the procedure described in Example 3, but using 0.9 g of 8'-O-isovaleryl-MB-530A, 10 ml of butanol and 1.0 g of the ion exchange resin, there was obtained 0.52 g of the desired product as a colourless oily substance.

20 Elemental analysis:

Calculated for $C_{27}H_{44}O_6$: C, 69.83%; H, 9.48%.

Found: C, 69.77%; H, 9.46%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

25 0.89 (1H, doublet);

1.24 (3H, triplet);

4.12 (2H, triplet);

3.5—4.5 (2H, multiplet);

Infrared Absorption Spectrum (liquid film) ν_{max} cm⁻¹:

3430, 1730.

20

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25

Example 9**Benzyl 8'-O-butyryl-ML-236A-carboxylate**

1.0 g of sodium 8'-O-butyryl-ML-236A-carboxylate was dissolved in 5 ml of dimethylformamide, and 1 ml of benzyl chloride was added thereto. The mixture was left to stand overnight. The reaction mixture was then diluted with water and extracted with ethyl acetate. The organic layer was separated, washed with water and dried over anhydrous sodium sulphate. The solvent was distilled off under reduced pressure and the residue was purified by column chromatography through silica gel, to afford 1.2 g of the desired product as a colourless oily substance.

35 Elemental analysis:

Calculated for $C_{29}H_{40}O_6$: C, 71.90%; H, 8.26%.

40 Found: C, 71.84%, H, 8.25%.

30

35

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

40 0.94 (3H, triplet);

1.24 (3H, triplet);

4.11 (2H, triplet);

45 3.5—4.5 (2H, multiplet);

5.20 (2H, singlet);

7.42 (5H, singlet).

Infrared Absorption Spectrum (liquid film) ν_{max} cm⁻¹:

3540, 1730..

40

45

Example 10**Benzyl 8'-O-hexanoyl-ML-236A-carboxylate**

Following the procedure described in Example 8, but using 1.2 g of sodium 8'-O-hexanoyl-ML-236A-carboxylate and 1 ml of benzyl chloride, there were obtained 1.3 g of the desired product as a colourless oily substance.

55 Elemental analysis:

Calculated for $C_{31}H_{44}O_6$: C, 72.66%; H, 8.59%.

60 Found: C, 72.58%; H, 8.50%.

50

55

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

55 0.89 (3H, triplet);

4.14 (2H, triplet);

3.5—4.5 (2H, multiplet);

60

5.21 (2H, singlet);
7.44 (5H, singlet).

Infrared Absorption Spectrum (liquid film) ν_{\max} cm⁻¹:
3400, 1730.

5

5 Example 11

Phenacyl 8'-O-butyryl-MB-530A-carboxylate

Following the procedure described in Example 8, but using 0.86 g of sodium 8'-O-butyryl-MB-530A-carboxylate and 0.45 g of phenacyl bromide, there was obtained 1.0 g of the desired product as a colourless oily substance.

10

Elemental analysis:

Calculated for C₂₁H₄₂O₇: C, 70.72%; H, 7.98%.
Found: C, 70.65%; H, 8.04%.

Nuclear Magnetic Resonance Spectrum (CDCl₃) δ ppm:

0.95 (3H, triplet);

4.13 (2H, triplet);

3.5—4.5 (2H, multiplet);

5.44 (2H, singlet);

7.4—8.2 (5H, multiplet).

15

Infrared Absorption Spectrum (liquid film) ν_{\max} cm⁻¹:

3450, 1730, 1700.

20

Example 12

Butyl 3,5-di(O-acetyl)-ML-236B-carboxylate

0.32 g of butyl ML-236B-carboxylate was dissolved in 1 ml of pyridine. After the addition of 1 ml of acetic anhydride, the mixture was left to stand at room temperature for 1 hour. The reaction mixture was then diluted with water and extracted with ethyl acetate. The solvent was distilled under reduced pressure from the extract and the residue was purified by column chromatography through silica gel, to afford 0.35 g of the desired product as a colourless oily substance.

25

Elemental analysis:

Calculated for C₃₁H₄₈O₈: C, 67.88%; H, 8.76%.
Found: C, 67.74%; H, 8.81%.

30

Nuclear Magnetic Resonance Spectrum (CDCl₃) δ ppm:

2.00 (3H, singlet);

2.03 (3H, singlet).

35

Infrared Absorption Spectrum (liquid film) ν_{\max} cm⁻¹:

1740.

35

Example 13

Butyl 3,5-di(O-benzoyl)-ML-236B-carboxylate

Following the procedure described in Example 11, but using 0.34 g of butyl ML-236B-carboxylate, 0.3 ml of benzoyl chloride and 1 ml of pyridine, there was obtained 0.38 g of the desired product as a colourless oily substance.

40

Elemental analysis:

Calculated for C₄₁H₅₂O₈: C, 73.21%; H, 7.74%.
Found: C, 73.10%; H, 7.89%.

45

Nuclear Magnetic Resonance Spectrum (CDCl₃) δ ppm:

7.2—7.6 (3H, multiplet);

7.8—8.2 (2H, multiplet).

45

Infrared Absorption Spectrum (liquid film) ν_{\max} cm⁻¹:

1720.

50

Example 14

Sodium ML-236A-carboxylate

300 litres of a culture medium (pH 5.5 before sterilization) containing 2% w/v glucose, 0.1% w/v peptone ('Kyokuto' brand) and 3% w/v malt extract were charged into a 600 litre fermenter and inoculated with the organism *Penicillium citrinum* SANK 18767. Cultivation was continued at 26°C for 96 hours under aerobic conditions at an aeration rate of 300 litres per minute and agitation at 145 rotations per minute. The culture broth (containing the organism) was adjusted to pH 3.4 with 6N hydrochloric acid and extracted with 800 litres of ethyl acetate. The extract was washed with 200 litres of a saturated aqueous solution of sodium chloride and then concentrated by evaporation in a vacuum to 18 litres. The resulting solution was extracted with 600 litres of ethyl acetate. 50 g of trifluoroacetic acid were added to the extract and reacted at 80°C for 30 minutes. The reaction mixture was washed successively with 20 litres of a 2% w/v aqueous solution of sodium bicarbonate and 2C litres of a 10% w/v aqueous solution of sodium chloride, after which it was concentrated by

55

60

evaporation under reduced pressure, to give 130 g of an oily substance. This oil was dissolved in 400 ml of methanol. 20 ml of the methanolic solution (containing 6.5 g of the oil) were subjected to preparative rapid liquid chromatography, System 500 type (produced by Waters Co., Ltd.) equipped with a Prepac C₁₈ column (reversed phase column). A mixture of methanol and water (60:40 v/v) was used as the developer. The development was carried out at a flow rate of 200 ml/minute (developing time: about 10 minutes), watching a differential refractometer connected to the apparatus, the portion showing a main peak on the differential refractometer was separated. This operation was repeated and resulting main peak fractions were collected and concentrated to give 9.2 g of an oily substance, which was dissolved in 30 ml of methanol. 6 ml of the methanolic solution (containing about 1.8 g of the oil) were subjected again to the same chromatography but developed with a 55:45 v/v mixture of methanol and water at a flow rate of 200 ml/minute. A portion showing a main peak was separated. This operation was repeated and the main peak fractions were collected and concentrated to afford 1020 mg of ML-236A as an oily substance. To this substance were added 33.2 ml of 0.1N aqueous solution of sodium hydroxide and the mixture was stirred at 50—60°C for 3 hours. Insolubles were filtered off and the filtrate was lyophilized, to give 1090 mg of sodium ML-236A-carboxylate.

Example 15**Sodium ML-236A-carboxylate**

1030 litres of an ethyl acetate extract from the culture broth obtained by the same procedures as described in Example 14 were washed with 200 litres of a saturated aqueous solution of sodium chloride. The extract was then dried over anhydrous sodium sulphate and concentrated to dryness to give 120 g of an oily substance containing ML-236A carboxylic acid. To this oil was added methanol to give a total volume of 200 ml. 20 ml of the solution was subjected to preparative rapid liquid chromatography equipped with a reversed phase column (the same as used in Example 14) and eluted with a 20% v/v aqueous methanol solution (containing 2% acetic acid) at a flow rate of 200 ml/minute. A portion showing a main peak on the differential refractometer was separated (7—10 minutes). The remaining 120 ml were treated by the same procedure. The resulting main peak fractions were collected, concentrated and extracted with ethyl acetate. The filtrate was concentrated to dryness after adding heptane, to give 8.7 g of an oily substance, which was dissolved in 20 ml of methanol and subjected to chromatography under the same conditions as above to give 930 mg of ML-236A carboxylic acid. To this product were added 2 ml of methanol and 100 ml of water and the resulting solution was adjusted to pH 8.0 with 1N aqueous sodium hydroxide to produce a clear aqueous solution, which was then lyophilized to give 980 mg of sodium ML-236A-carboxylate as a white powder.

Example 16

35 Sodium MB-530A-carboxylate

300 litres of a culture medium (pH 5.5 before sterilization) containing 5% w/v glucose, 0.5% w/v corn steep liquor, 2% w/v peptone ("Kyokuto" brand) and 0.5% w/v ammonium chloride were charged into a 600 litre fermenter and inoculated with the organism *Monascus ruber* SANK 18174. Cultivation was continued at 26°C for 116 hours under aerobic conditions at an aeration rate of 300 litres per minute and agitation at 190 rotations per minute. The culture broth (containing the organism) was adjusted to pH 3.4 with 6N hydrochloric acid and extracted with 800 litres of ethyl acetate. The extract was washed with 200 litres of a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulphate. It was then concentrated to 18 litres by evaporation under reduced pressure. The resulting solution was extracted with 600 litres of ethyl acetate. 50 g of trifluoroacetic acid were added to the extract and reacted at 80°C for 30 minutes. The reaction mixture was washed successively with 10 litres of a 2% w/v aqueous solution of sodium bicarbonate and 10 litres of a 10% w/v aqueous solution of sodium chloride, and then was concentrated to give 105 g of an oily substance. This oil was dissolved in 400 ml of methanol. 20 ml of the methanolic solution (containing about 5.3 g of the oil) were subjected to preparative rapid liquid chromatography with a reverse phase column (the same as in Example 14). A 65:35 v/v mixture of methanol and water was used as the developer. The development was carried out at a flow rate of 200 ml/minute (developing time: about 15 minutes), watching a differential refractometer connected to the apparatus, the portion showing a main peak on the differential refractometer was separated. This operation was repeated and the resulting main peak fractions were collected and concentrated to give 7.9 g of an oily substance, which was dissolved in 30 ml of methanol. 60 ml of this methanolic solution (containing about 1.6 g of the oil) were subjected again to the same chromatography but developed with a 60:40 v/v mixture of methanol and water at a flow rate of 200 ml/minute. A portion showing a main peak was separated. This operation was repeated and the main peak fractions were collected and concentrated. There were obtained 679 mg of MB-530A as an oily substance. To this substance were added 21 ml of a 0.1N aqueous solution of sodium hydroxide and the mixture was stirred at 50—60°C for 3 hours. Insolubles were filtered off and the filtrate was lyophilized to give 720 mg of sodium MB-530A-carboxylate.

Elemental analysis:

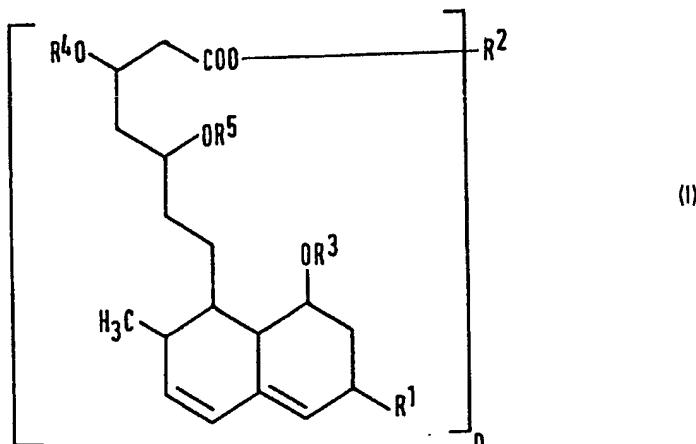
calculated for C₁₉H₂₉O₅Na: C, 63.33%; H, 8.06%.
Found: C, 63.51%; H, 7.97%.

Example 17**Sodium MB-530A-carboxylate**

300 litres of a culture medium (pH 7.4 before sterilization) containing 1.5% w/v soluble starch, 1.5% w/v glycerine, 2% w/v fish meal and 0.2% w/v calcium carbonate were charged into a 600 litre fermenter and inoculated with the organism *Monascus ruber* SANK 17075 (CBS 832.70). Cultivation was continued at a temperature of 26°C for 120 hours under aerobic conditions at an aeration rate of 300 litres per minute and agitation at 190 rotations per minute. The resulting culture broth was filtered using a filter press to give 35 kg of the wet organism, to which 100 litres of water were added. The mixture was adjusted to pH 12 with sodium hydroxide, with stirring, and left to stand at room temperature for 1 hour. 2 kg of Hyflo Super Cel filter aid were added to the mixture, which was filtered by a filter press. The filtrate was adjusted to pH 10 with hydrochloric acid and adsorbed on a column charged with 5 litres of HP-20 resin. It was then washed with 15 litres each of water and 10% v/v aqueous methanol, after which it was eluted with 60% v/v aqueous methanol. The eluate was concentrated to a volume of about 10 litres. The residue was adjusted to pH 2 with hydrochloric acid and extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulphate and concentrated to dryness to give 20 g of an oily substance containing MB-530A carboxylic acid. To this oil was added methanol to a total volume of 100 ml. 20 ml of the solution were subjected to preparative rapid liquid chromatography equipped with a reversed phase column (the same as used in Example 14) and eluted with a 13% v/v aqueous methanol solution (containing 2% acetic acid) at a flow rate of 200 ml/minute. A portion showing a main peak on the differential refractometer was separated (7—10 minutes). The remaining 80 ml were treated in the same manner. The resulting main peak fractions were collected, concentrated and extracted with ethyl acetate. The extract was concentrated to dryness after adding heptane, to give 920 mg of an oily substance, which was dissolved in 20 ml of methanol and subjected to chromatography under the same conditions as above to give 120 mg of MB-530A carboxylic acid. To this product were added 2 ml of methanol and 100 ml of water and the resulting solution was adjusted to pH 8.0 with 1N aqueous sodium hydroxide to produce a clear aqueous solution. This was lyophilized to give 110 mg of sodium MB-530A-carboxylate as a white powder.

Claims

30 1. Compounds of formula (I): 30



wherein:

R¹ represents a hydrogen atom or a methyl group;

R² represents a hydrogen atom, the alcoholic moiety of an ester of the cationic moiety of a salt; and

35 R³, R⁴ and R⁵ are the same or different and each represents a hydrogen atom or an organic or inorganic acyl group, provided that, when R³ represents a 2-methylbutyryl group, R⁴ and R⁵ both represent acyl groups.

2. Compounds as claimed in Claim 1, in which:

R¹ represents a hydrogen atom or a methyl group;

40 R² represents a hydrogen atom, a metal atom, an ammonium group, an alkyl-substituted ammonium group, a group capable of forming a salt derived from a basic amino acid, an alkyl group, an aralkyl group optionally having a substituent on the aryl moiety or a phenacyl group optionally having a substituent on the phenyl moiety, said substituents being selected from C₁—C₄ alkyl groups, C₁—C₄ alkoxy groups, halogen atoms and trifluoromethyl groups; and

45 R³, R⁴ and R⁵ are the same or different and each represents a hydrogen atom, an aliphatic acyl

group, an aromatic acyl group or an araliphatic acyl group, provided that, when R³ represents a 2-methylbutyryl group, R⁴ and R⁵ both represent acyl groups.

3. Compounds as claimed in Claim 1, in which:

R¹ represents a hydrogen atom or a methyl group;

5 R² represents a hydrogen atom, an alkali metal atom, an alkaline earth metal atom, aluminium, zinc, iron, germanium, an ammonium group, a group capable of forming a salt derived from a basic amino acid, a C₁—C₈ alkyl group, an aralkyl group optionally having a substituent on the aryl moiety, or a phenacyl group optionally having a substituent on the phenyl moiety, said substituent being selected from C₁—C₄ alkyl groups, C₁—C₄ alkoxy groups, halogen atoms, and trifluoromethyl groups; and

10 R³, R⁴ and R⁵ are the same or different and each represents a hydrogen atom, a C₂—C₂₀ alkanoyl group, a C₃—C₂₀ alkenoyl group, a C₃—C₂₀ alkynoyl group, a C₇—C₁₅ aromatic acyl group, a C₈—C₉ aralkenoyl group or a C₈ aralkenoyl group, provided that, when R³ represents a 2-methylbutyryl group, R⁴ and R⁵ both represent acyl groups.

4. Compounds as claimed in Claim 1, in which:

15 R¹ represents a hydrogen atom or a methyl group;

R² represents a hydrogen atom, an alkali metal atom, an alkaline earth metal atom, an ammonium group, a group capable of forming a salt derived from a basic amino acid, a C₁—C₄ alkyl group, a benzyl group or a phenacyl group; and

20 R³, R⁴ and R⁵ are the same or different and each represents a hydrogen atom, a C₂—C₆ alkanoyl group, a C₃—C₆ alkenoyl group or a benzoyl group, provided that, when R³ represents a 2-methylbutyryl group, R⁴ and R⁵ both represent acyl groups.

5. Compounds as claimed in Claim 1, in which:

R¹ represents a hydrogen atom or a methyl group;

25 R² represents a C₁—C₄ alkyl group, a benzyl group or a phenacyl group;

R³ represents a C₂—C₆ alkanoyl group or a C₃—C₆ alkenoyl group; and

R⁴ and R⁵ are the same or different and each represents a C₂—C₆ alkanoyl group or a benzoyl group.

6. Compounds as claimed in Claim 1, in which:

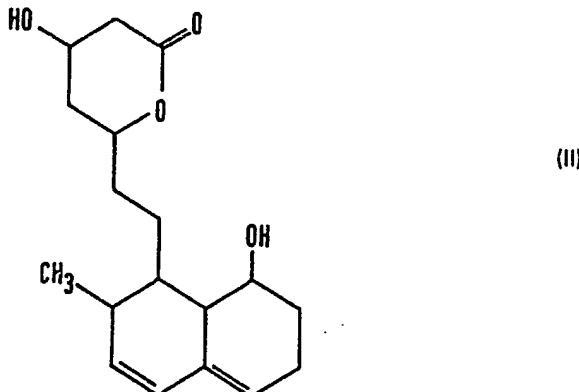
30 R¹ represents a hydrogen atom;

R² represents a C₁—C₄ alkyl group;

R³ represents a C₂—C₆ alkanoyl group; and

R⁴ and R⁵ are the same or different and each represents an acetyl group or a benzoyl group.

7. Compounds of formula (II):



35 wherein:

35

R¹ represents a hydrogen atom or a methyl group;

R^{2a} represents a hydrogen atom, an alkali metal atom, an alkaline earth metal atom, an ammonium group, a group capable of forming a salt derived from a basic amino acid, a C₁—C₄ alkyl group, a benzyl group or a phenacyl group;

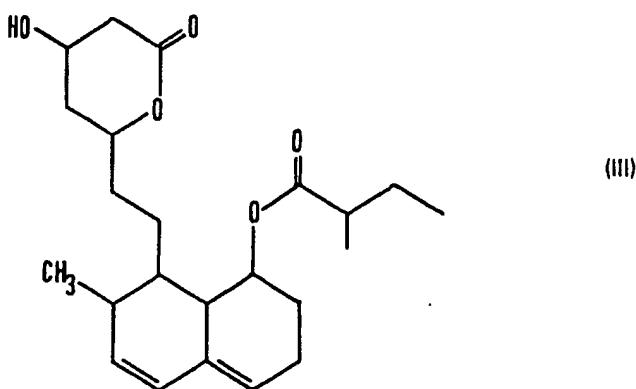
40 R^{3a} represents a C₂—C₆ alkanoyl group other than a 2-methylbutyryl group or a C₃—C₆ alkenoyl group; and

m represents the valence of R^{2a}.

8. Compounds as claimed in Claim 7, in which R^{2a} represents a C₁—C₄ alkyl group, a benzyl group or a phenacyl group.

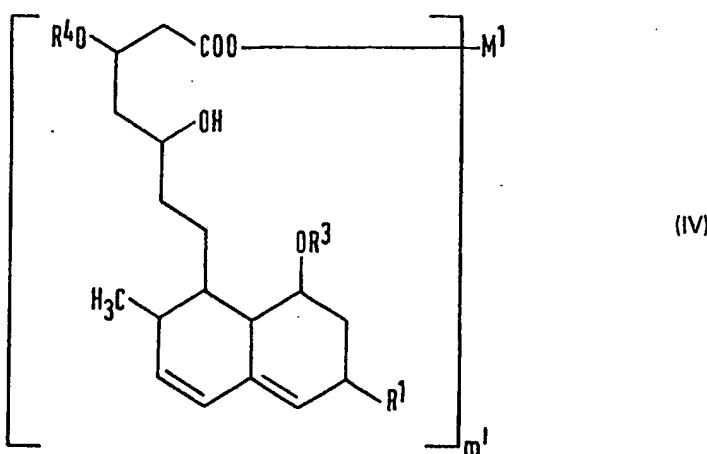
45 9. Compounds as claimed in Claim 7, in which R^{2a} represents an alkali metal atom.

10. Compounds of formula (III):



wherein:

R¹ represents a hydrogen atom or a methyl group; and M represents a hydrogen atom or an alkali metal atom.



(wherein:

R^1 represents a hydrogen atom or a methyl group;

R^3 and R^4 are the same or different and each represents a hydrogen atom or an acyl group,

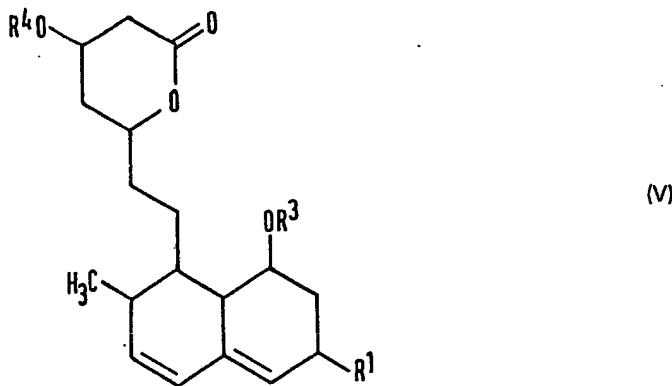
5 provided that, when R^3 represents a 2-methylbutyryl group, R^4 represents an acyl group;

5

M^1 represents the cationic moiety of a salt; and

m' is the valence of M^1),

in which a lactone compound of formula (V):



10 (wherein R^1 , R^3 , R^4 , M^1 and m' are as defined above) is hydrolyzed and, if desired, the carboxy group of 10
the product thus obtained is converted to the corresponding salt.

36. A process as claimed in Claim 35, in which said hydrolysis is effected in an alkali solution and
15 M^1 represents an alkali metal atom.

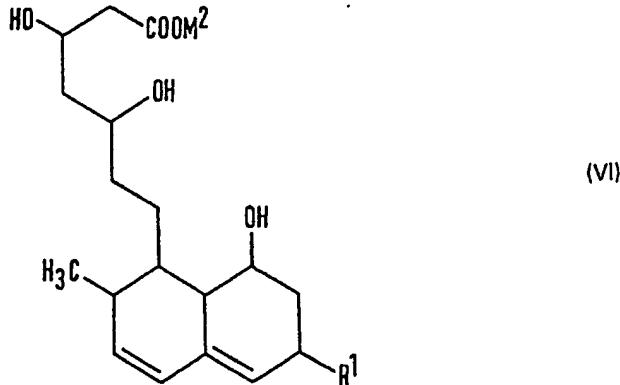
37. A process as claimed in Claim 35 or Claim 36, in which:

15 R^1 represents a hydrogen atom or a methyl group;

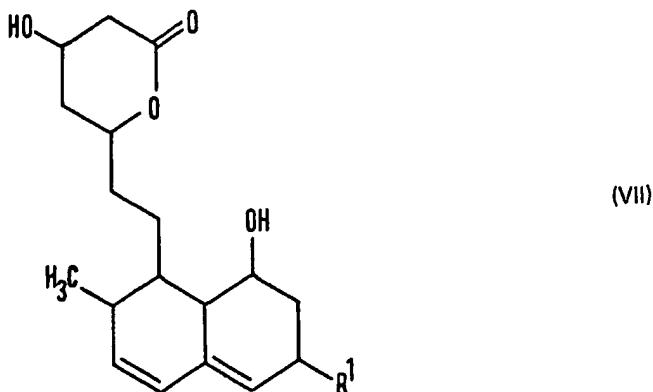
R^3 represents a hydrogen atom, a C_2 — C_6 alkanoyl group or a C_3 — C_6 alkenoyl group; and

R^4 represents a hydrogen atom, a C_2 — C_6 alkanoyl group or a benzoyl group.

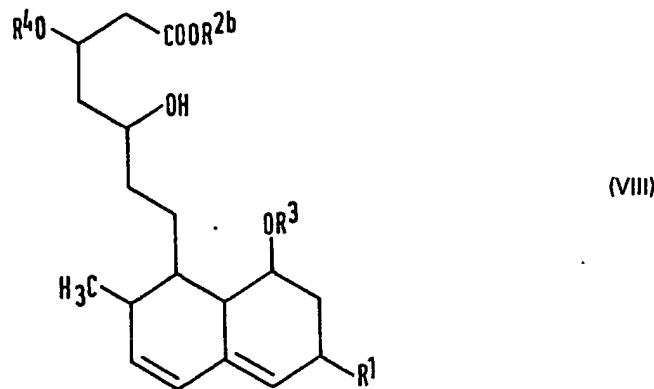
38. A process for preparing a carboxylic acid derivative of formula (VI):



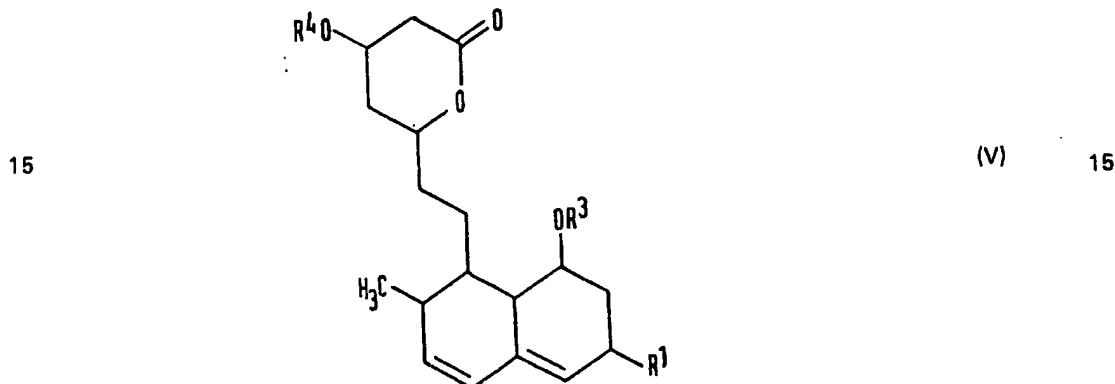
(wherein R¹ represents a hydrogen atom or a methyl group and M² represents an alkali metal atom) in which a compound of formula (VII):



5 (wherein R¹ is as defined above) is hydrolyzed in an alkali solution.
 5 39. A process as claimed in Claim 38, in which M² represents a sodium atom and said alkali solution is an aqueous solution of sodium hydroxide.
 40. A process for preparing a carboxylic acid ester of formula (VIII):



10 (wherein:
 10 R¹ represents a hydrogen atom or a methyl group;
 R³ and R⁴ are the same or different and each represents a hydrogen atom or an acyl group,
 provided that, when R³ represents a 2-methylbutyryl group, R⁴ represents an acyl group; and
 R^{2b} represents an alkyl group or an aralkyl group),
 in which a lactone compound of formula (V):



(wherein R¹, R³ and R⁴ are as defined above) is reacted with an alcohol in the presence of an acid catalyst.

41. A process as claimed in Claim 40, in which said acid catalyst is an inorganic acid, a Lewis acid or a cation exchange resin.

42. A process as claimed in Claim 41, in which said acid catalyst is a strongly acidic cation exchange resin.

43. A process as claimed in any one of Claims 40 to 42, in which:

R¹ represents a hydrogen atom or a methyl group;

5 R³ represents a hydrogen atom, a C₂—C₆ alkanoyl group or a C₃—C₆ alkenoyl group; 5

R⁴ represents a hydrogen atom, a C₂—C₆ alkanoyl group or a benzoyl group (provided that, when

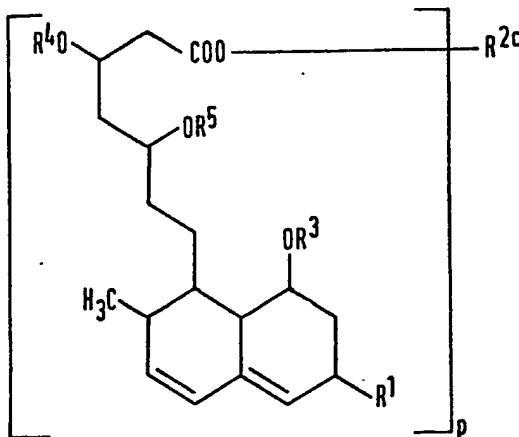
R³ represents a 2-methylbutyryl group, R⁴ represents an acyl group); and

44. A process for preparing a carboxylic acid ester of formula (IX):

10

(IX)

10



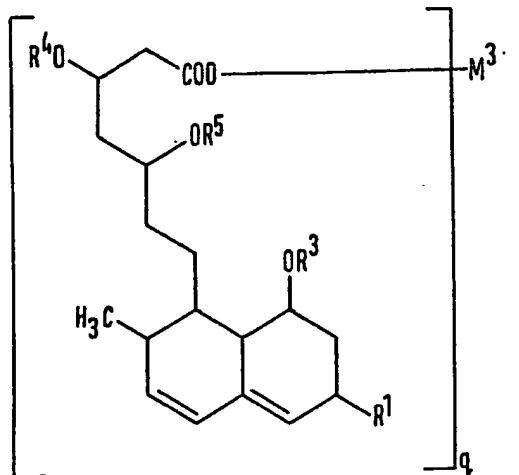
(wherein:

R¹, R³, R⁴ and R⁵ are as defined in Claim 1;

R^{2c} represents the alcoholic moiety of an ester; and

p is the valence of R^{2c}),

15 In which a carboxylic acid salt of formula (X): 15



(wherein R¹, R³, R⁴ and R⁵ are as defined above, M³ represents an alkali or alkaline earth metal atom, and q is the valence of M³) is reacted with an esterifying agent.

45. A process as claimed in Claim 44, in which said esterifying agent is an alkyl halide, an aralkyl halide or a phenacyl halide. 20

46. A process as claimed in Claim 44 or Claim 45, in which M³ represents an alkali metal atom.

47. A process as claimed in Claim 46, in which said salt (X) in which M³ represents an alkali metal atom is formed *in situ* prior to said reaction with an esterifying agent.

48. A process as claimed in any one of Claims 44 to 47, in which:

25 R¹ represents a hydrogen atom or a methyl group; 25

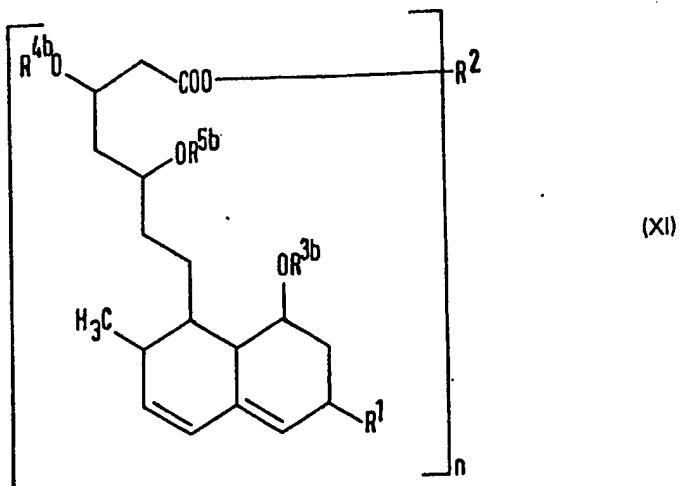
R³ represents a hydrogen atom, a C₂—C₆ alkanoyl group or a C₃—C₆ alkenoyl group;

R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_2-C_6 alkanoyl group or a benzoyl group, provided that, when R^3 represents a 2-methylbutyryl group, R^4 and R^5 both represent acyl groups;

M^3 represents an alkali metal atom; and

5 said esterifying agent is a benzyl halide or a phenacyl halide.

49. A process for preparing a triacyl compound of formula (XI):

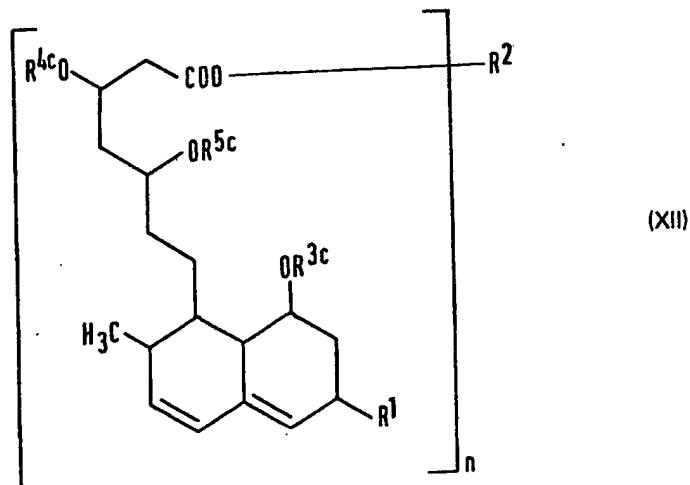


(wherein:

R^1 , R^2 and n are as defined in Claim 1; and

10 R^{3b} , R^{4b} and R^{5b} are the same or different and each represents an acyl group),

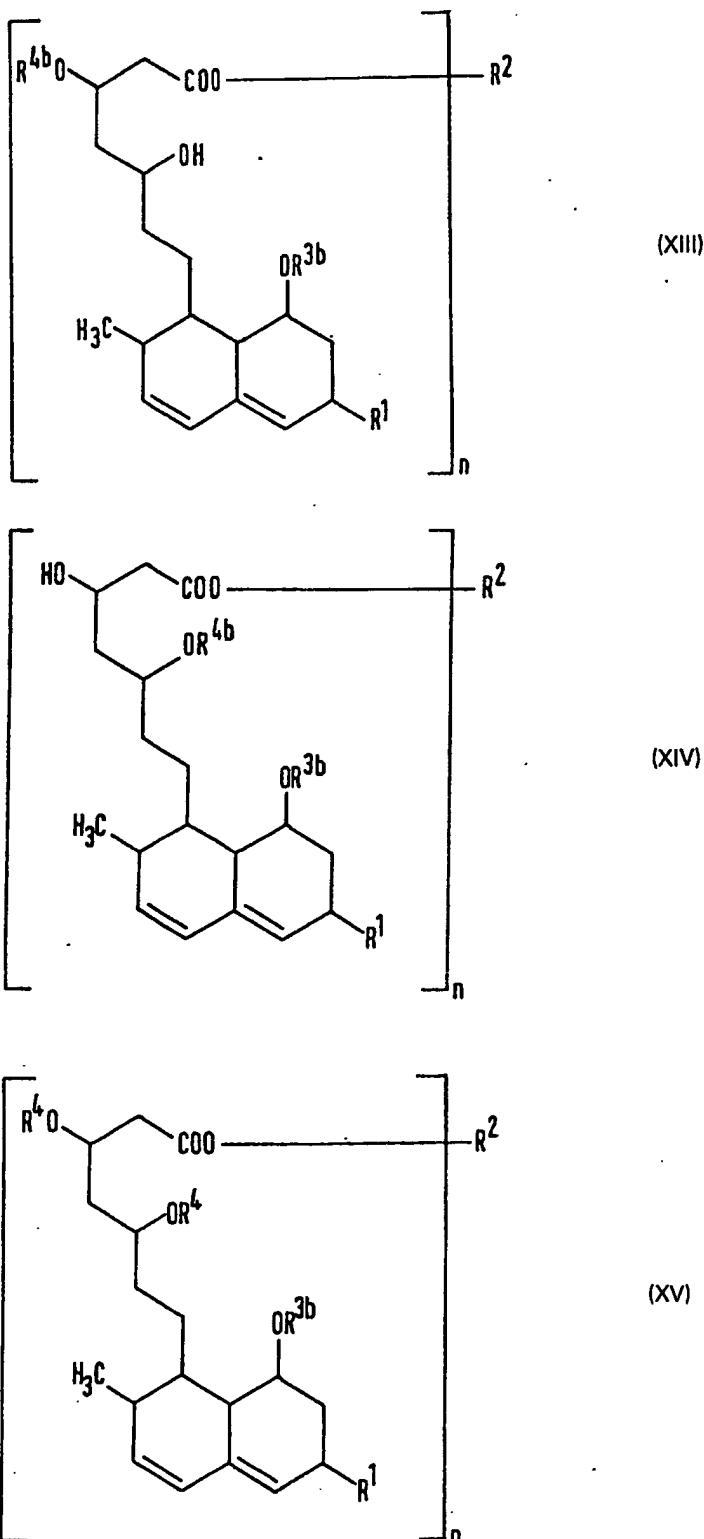
in which a compound of formula (XII):



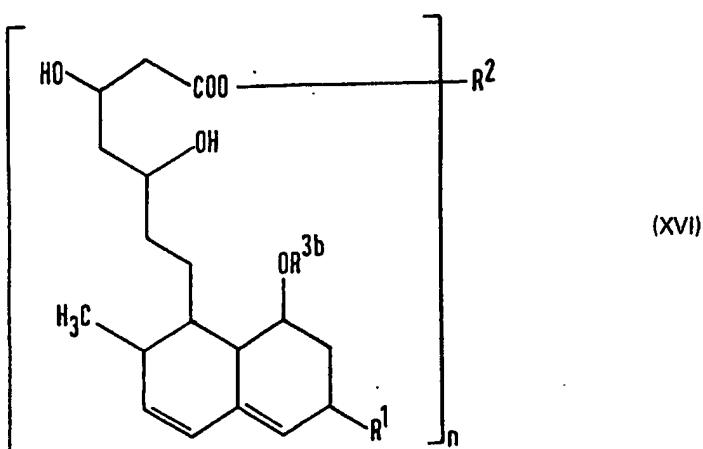
(wherein R^1 , R^2 and n are as defined above and R^{3c} , R^{4c} and R^{5c} are the same or different and each represents a hydrogen atom or an acyl group provided that at least one of R^{3c} , R^{4c} and R^{5c} represents a

15 hydrogen atom) is acylated.

50. A process for preparing one or more compounds of formulae (XIII), (XIV) and (XV):



(wherein:
 5 R^1 , R^2 , R^4 and n are as defined in Claim 1;
 R^{3b} represents an acyl group; and
 R^{4b} represents an acyl group),
 in which a compound of formula (XVI):



(wherein R¹, R², R^{3b} and n are as defined above) is acylated to produce compounds of said formulae (XIII), (XIV) or (XV) and they are isolated from the reaction mixture.

51. A process as claimed in Claim 50, in which, in said compound (XVI):

5 R¹ represents a hydrogen atom or a methyl group;
 R² represents an alkali metal atom, a C₁—C₄ alkyl group, a benzyl group or a phenacyl group; and
 R^{3b} represents a C₂—C₈ alkanoyl group or a C₃—C₆ alkenoyl group,
 said acylation is effected with a C₂—C₈ alcanoic acid, benzoic acid or a reactive derivative thereof, and
 there is produced said compounds (XIII) and/or (XIV) in which R^{4b} represents an alkanoyl group or a
 10 benzoyl group.

52. A process as claimed in Claim 50, in which said acylation is effected with a reactive derivative
 of a carboxylic or sulphonic acid.

53. A process as claimed in Claim 52, in which said acylation is effected with an acid halide, an
 acid anhydride or a mixed anhydride of a carboxylic or sulphonic acid.

15 54. A process for preparing compounds of formula (I), as defined in Claim 1, substantially as
 hereinbefore described with reference to any one of the foregoing Examples.